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(54) Title: MODIFIED TRANSFERRIN FUSION PROTEINS

(57) Abstract: Modified fusion proteins of transferrin and therapeutic proteins or peptides with increased serum half-life or serum stability are disclosed. Preferred fusion proteins include those modified so that the transferrin moiety exhibits no or reduced glyco-  
sylation, binding to iron and/or binding to the transferrin receptor.



**WO 03/020746 A1**

**MODIFIED TRANSFERRIN FUSION PROTEINS****INVENTOR: Christopher P. Prior****RELATED APPLICATIONS**

This application claims priority to U.S. provisional application 60/315,745, filed August 30, 2001 and U.S. provisional application 60/334,059, filed November 30, 2001, both of which are herein incorporated by reference in their entirety.

5

**FIELD OF THE INVENTION**

The present invention relates to therapeutic proteins or peptides with extended serum stability or serum half-life, particularly to therapeutic proteins or peptides fused to or inserted in a transferrin molecule modified to reduce or inhibit glycosylation, iron binding and/or transferrin receptor binding.

10

**BACKGROUND OF THE INVENTION**

Therapeutic proteins or peptides in their native state or when recombinantly produced are typically labile molecules exhibiting short periods of serum stability or short serum half-lives. In addition, these molecules are often extremely labile when formulated, particularly when formulated in aqueous solutions for diagnostic and therapeutic purposes.

15

Few practical solutions exist to extend or promote the stability *in vivo* or *in vitro* of proteinaceous therapeutic molecules. Polyethylene glycol (PEG) is a substance that can attach to a protein, resulting in longer-acting, sustained activity of the protein. If the activity of a protein is prolonged by the attachment to PEG, the frequency that the protein needs to be administered is decreased. PEG attachment, however, often decreases or destroys the protein's therapeutic activity.

20

Therapeutic proteins or peptides have also been stabilized by fusion to a heterologous protein capable of extending the serum half-life of the therapeutic protein. For instance, therapeutic proteins fused to albumin and antibody fragments may exhibit extended serum half-life when compared to the therapeutic protein in the unfused state. See U.S. Patents 5,876,969 and 5,766,88.

25

Another serum protein, glycosylated human transferrin (Tf) has also been used to make fusions with therapeutic proteins to target delivery intracellularly or to carry heterologous agents across the blood-brain barrier. These fusion proteins comprising glycosylated human Tf have been used to target nerve growth factor (NGF) or ciliary neurotrophic factor (CNTF) across the blood-brain barrier by fusing full-length Tf

30

to the either agent. See U.S. Patents 5,672,683 and 5,977,307. In these fusion proteins, the Tf portion of the molecule is glycosylated and binds to two atoms of iron, which is required for Tf binding to its receptor on a cell and, according to the inventors of these patents, to target delivery of the NGF or CNTF moiety across the blood-brain barrier.

5 Transferrin fusion proteins have also been produced by inserting an HIV-1 protease sequence into surface exposed loops of glycosylated transferrin to investigate the ability to produce another form of Tf fusion for targeted delivery to the inside of a cell via the Tf receptor (Ali *et al.* (1999) *J. Biol. Chem.* 274(34):24066-24073).

Serum transferrin (Tf) is a monomeric glycoprotein with a molecular weight of  
10 80,000 daltons that binds iron in the circulation and transports it to various tissues via the transferrin receptor (TfR) (Aisen *et al.* (1980) *Ann. Rev. Biochem.* 49: 357-393; MacGillivray *et al.* (1981) *J. Biol. Chem.* 258: 3543-3553, U.S. Patent 5,026,651). Tf is one of the most common serum molecules, comprising up to about 5-10% of total serum proteins. Carbohydrate deficient transferrin occurs in elevated levels in the blood of  
15 alcoholics and exhibits a longer half life (approximately 14-17 days) than that of glycosylated transferrin (approximately 7-10 days). See van Eijk *et al.* (1983) *Clin. Chim. Acta* 132:167-171, Stibler (1991) *Clin. Chem.* 37:2029-2037 (1991), Arndt (2001) *Clin. Chem.* 47(1):13-27 and Stibler *et al.* in "Carbohydrate-deficient consumption", *Advances in the Biosciences*, (Ed Nordmann *et al.*), Pergamon, 1988, Vol. 71, pages 353-357).

20 The structure of Tf has been well characterized and the mechanism of receptor binding, iron binding and release and carbonate ion binding have been elucidated (U.S. Patents 5,026,651, 5,986,067 and MacGillivray *et al.* (1983) *J. Biol. Chem.* 258(6):3543-3546).

Transferrin and antibodies that bind the transferrin receptor have also been used to  
25 deliver or carry toxic agents to tumor cells as cancer therapy (Baselga and Mendelsohn, 1994), and transferrin has been used as a non-viral gene therapy vector to vehicle to deliver DNA to cells (Frank *et al.*, 1994; Wagner *et al.*, 1992). The ability to deliver proteins to the central nervous system (CNS) using the transferrin receptor as the entry point has been demonstrated with several proteins and peptides including CD4 (Walus *et al.*, 1996), brain derived neurotrophic factor (Pardridge *et al.*, 1994), glial derived  
30 neurotrophic factor (Albeck *et al.*), a vasointestinal peptide analogue (Bickel *et al.*, 1993), a betaamyloid peptide (Saito *et al.*, 1995), and an antisense oligonucleotide (Pardridge *et al.*, 1995).

Transferrin fusion proteins have not, however, been modified or engineered to extend the serum half-life of a therapeutic protein or peptide or to increase bioavailability by reducing or inhibiting glycosylation of the Tf moiety or to reduce or prevent iron and/or Tf receptor binding.

5

## SUMMARY OF THE INVENTION

As described in more detail below, the present invention includes modified Tf fusion proteins comprising at least one therapeutic protein, polypeptide or peptide entity, wherein the Tf portion is engineered to extend the serum half-life or bioavailability of the molecule. The invention also includes pharmaceutical formulations and compositions comprising the fusion proteins, methods of extending the serum stability, serum half-life and bioavailability of a therapeutic protein by fusion to modified transferrin, nucleic acid molecules encoding the modified Tf fusion proteins, and the like. Another aspect of the present invention relates to methods of treating a patient with a modified Tf fusion protein.

15 In a preferred embodiment, the modified Tf fusion proteins comprise a human transferrin Tf moiety that has been modified to reduce or prevent glycosylation and/or iron and receptor binding.

## BRIEF DESCRIPTION OF THE DRAWINGS

20 **Figure 1** shows an alignment of the N and C Domains of Human (Hu) transferrin (Tf) with similarities and identities highlighted.

**Figure 2A-2B** shows an alignment of transferrin sequences from different species. Light shading: Similarity; Dark shading: Identity

**Figure 3** shows the location of a number of Tf surface exposed insertion sites for therapeutic proteins, polypeptides or peptides.

25 **Figure 4A-4B** shows the VH and VL regions for a number of preferred anti-TNF $\alpha$  antibodies used to produce modified Tf fusion proteins.

**Figure 5** shows pREX0010

**Figure 6** shows pREX0011

30 **Figure 7** shows pREX0012

**Figure 8** shows pREX0013

**Figure 9** shows pREX0014

**Figure 10** shows pREX0015



## DETAILED DESCRIPTION

### General Description

It has been discovered that a therapeutic protein (*e.g.*, a polypeptide, antibody, or peptide, or fragments and variants thereof) can be stabilized to extend the serum half-life and/or retain the therapeutic protein's activity for extended periods of time *in vivo* by genetically fusing or chemically conjugating the therapeutic protein, polypeptide or peptide to all or a portion of modified transferrin sufficient to extend its half life in serum. The modified transferrin fusion proteins include a transferrin protein or domain covalently linked to a therapeutic protein or peptide, wherein the transferrin portion is modified to contain one or more amino acid substitutions, insertions or deletions compared to a wild-type transferrin sequence. In one embodiment, Tf fusion proteins are engineered to reduce or prevent glycosylation within the Tf or a Tf domain. In other embodiments, the Tf protein or Tf domain(s) is modified to exhibit reduced or no binding to iron or carbonate ion, or to have a reduced affinity or not bind to a Tf receptor (TfR).

The present invention therefore includes transferrin fusion proteins, therapeutic compositions comprising the fusion proteins, and methods of treating, preventing, or ameliorating diseases or disorders by administering the fusion proteins. A transferrin fusion protein of the invention includes at least a fragment or variant of a therapeutic protein and at least a fragment or variant of modified transferrin, which are associated with one another, preferably by genetic fusion (*i.e.*, the transferrin fusion protein is generated by translation of a nucleic acid in which a polynucleotide encoding all or a portion of a therapeutic protein is joined in-frame with a polynucleotide encoding all or a portion of modified transferrin) or chemical conjugation to one another. The therapeutic protein and transferrin protein, once part of the transferrin fusion protein, may be referred to as a "portion", "region" or "moiety" of the transferrin fusion protein (*e.g.*, a "therapeutic protein portion" or a "transferrin protein portion").

In one embodiment, the invention provides a transferrin fusion protein comprising, or alternatively consisting of, a therapeutic protein and a modified serum transferrin protein. In other embodiments, the invention provides a transferrin fusion protein comprising, or alternatively consisting of, a biologically active and/or therapeutically active fragment of a therapeutic protein and a modified transferrin protein. In other embodiments, the invention provides a transferrin fusion protein comprising, or

alternatively consisting of, a biologically active and/or therapeutically active variant of a therapeutic protein and modified transferrin protein. In further embodiments, the invention provides a transferrin fusion protein comprising a therapeutic protein, and a biologically active and/or therapeutically active fragment of modified transferrin. In another embodiment, the therapeutic protein portion of the transferrin fusion protein is the active form of the therapeutic protein.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods and materials are described.

### Definitions

As used herein, the term “biological activity” refers to a function or set of activities performed by a therapeutic molecule, protein or peptide in a biological context (*i.e.*, in an organism or an *in vitro* facsimile thereof). Biological activities may include but are not limited to the functions of the therapeutic molecule portion of the claimed fusion proteins, such as, but not limited to, the induction of extracellular matrix secretion from responsive cell lines, the induction of hormone secretion, the induction of chemotaxis, the induction of mitogenesis, the induction of differentiation, or the inhibition of cell division of responsive cells. A fusion protein or peptide of the invention is considered to be biologically active if it exhibits one or more biological activities of its therapeutic protein’s native counterpart.

As used herein, an “amino acid corresponding to” or an “equivalent amino acid” in a transferrin sequence is identified by alignment to maximize the identity or similarity between a first transferrin sequence and at least a second transferrin sequence. The number used to identify an equivalent amino acid in a second transferrin sequence is based on the number used to identify the corresponding amino acid in the first transferrin sequence. In certain cases, these phrases may be used to describe the amino acid residues in human transferrin compared to certain residues in rabbit serum transferrin.

As used herein, the terms “fragment of a Tf protein” or “Tf protein,” or “portion of a Tf protein” refer to an amino acid sequence comprising at least about 5%, 10%, 20%,

30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, 96%, 97%, 98%, 99% or 100% of a naturally occurring Tf protein or mutant thereof.

As used herein, the term “gene” refers to any segment of DNA associated with a biological function. Thus, genes include, but are not limited to, coding sequences and/or the regulatory sequences required for their expression. Genes can also include nonexpressed DNA segments that, for example, form recognition sequences for other proteins. Genes can be obtained from a variety of sources, including cloning from a source of interest or synthesizing from known or predicted sequence information, and may include sequences designed to have desired parameters.

As used herein, a “heterologous polynucleotide” or a “heterologous nucleic acid” or a “heterologous gene” or a “heterologous sequence” or an “exogenous DNA segment” refers to a polynucleotide, nucleic acid or DNA segment that originates from a source foreign to the particular host cell, or, if from the same source, is modified from its original form. A heterologous gene in a host cell includes a gene that is endogenous to the particular host cell, but has been modified. Thus, the terms refer to a DNA segment which is foreign or heterologous to the cell, or homologous to the cell but in a position within the host cell nucleic acid in which the element is not ordinarily found. As an example, a signal sequence native to a yeast cell but attached to a human Tf sequence is heterologous.

As used herein, an “isolated” nucleic acid sequence refers to a nucleic acid sequence which is essentially free of other nucleic acid sequences, *e.g.*, at least about 20% pure, preferably at least about 40% pure, more preferably about 60% pure, even more preferably about 80% pure, most preferably about 90% pure, and even most preferably about 95% pure, as determined by agarose gel electrophoresis. For example, an isolated nucleic acid sequence can be obtained by standard cloning procedures used in genetic engineering to relocate the nucleic acid sequence from its natural location to a different site where it will be reproduced. The cloning procedures may involve excision and isolation of a desired nucleic acid fragment comprising the nucleic acid sequence encoding the polypeptide, insertion of the fragment into a vector molecule, and incorporation of the recombinant vector into a host cell where multiple copies or clones of the nucleic acid sequence will be replicated. The nucleic acid sequence may be of genomic, cDNA, RNA, semisynthetic, synthetic origin, or any combinations thereof.

As used herein, two or more DNA coding sequences are said to be “joined” or “fused” when, as a result of in-frame fusions between the DNA coding sequences, the

DNA coding sequences are translated into a polypeptide fusion. The term “fusion” in reference to Tf fusions includes, but is not limited to, attachment of at least one therapeutic protein, polypeptide or peptide to the N-terminal end of Tf, attachment to the C-terminal end of Tf, and/or insertion between any two amino acids within Tf.

5 “Modified transferrin” as used herein refers to a transferrin molecule that exhibits at least one modification of its amino acid sequence, compared to wildtype transferrin.

“Modified transferrin fusion protein” as used herein refers to a protein formed by the fusion of at least one molecule of modified transferrin (or a fragment or variant thereof) to at least one molecule of a therapeutic protein (or fragment or variant thereof).

10 As used herein, the terms “nucleic acid” or “polynucleotide” refer to deoxyribonucleotides or ribonucleotides and polymers thereof in either single- or double-stranded form. Unless specifically limited, the terms encompass nucleic acids containing analogues of natural nucleotides that have similar binding properties as the reference nucleic acid and are metabolized in a manner similar to naturally occurring nucleotides.

15 Unless otherwise indicated, a particular nucleic acid sequence also implicitly encompasses conservatively modified variants thereof (*e.g.* degenerate codon substitutions) and complementary sequences as well as the sequence explicitly indicated. Specifically, degenerate codon substitutions may be achieved by generating sequences in which the third position of one or more selected (or all) codons is substituted with mixed-base and/or  
20 deoxyinosine residues (Batzer *et al.* (1991) *Nucleic Acid Res.* 19:5081; Ohtsuka *et al.* (1985) *J. Biol. Chem.* 260:2605-2608; Cassol *et al.* (1992); Rossolini *et al.* (1994) *Mol. Cell. Probes* 8:91-98). The term nucleic acid is used interchangeably with gene, cDNA, and mRNA encoded by a gene.

As used herein, a DNA segment is referred to as “operably linked” when it is  
25 placed into a functional relationship with another DNA segment. For example, DNA for a signal sequence is operably linked to DNA encoding a fusion protein of the invention if it is expressed as a preprotein that participates in the secretion of the fusion protein; a promoter or enhancer is operably linked to a coding sequence if it stimulates the transcription of the sequence. Generally, DNA sequences that are operably linked are  
30 contiguous, and in the case of a signal sequence or fusion protein both contiguous and in reading phase. However, enhancers need not be contiguous with the coding sequences whose transcription they control. Linking, in this context, is accomplished by ligation at convenient restriction sites or at adapters or linkers inserted in lieu thereof.

As used herein, the term “promoter” refers to a region of DNA involved in binding RNA polymerase to initiate transcription.

As used herein, the term “recombinant” refers to a cell, tissue or organism that has undergone transformation with recombinant DNA.

5 As used herein, a targeting entity, protein, polypeptide or peptide refers to such molecules that binds specifically to a particular cell type [normal (*e.g.*, lymphocytes) or abnormal *e.g.*, (cancer cell)] and therefore may be used to target a Tf fusion protein or compound (drug, or cytotoxic agent) to that cell type specifically.

As used herein, “therapeutic protein” refers to proteins, polypeptides, antibodies,  
10 peptides or fragments or variants thereof, having one or more therapeutic and/or biological activities. Therapeutic proteins encompassed by the invention include but are not limited to proteins, polypeptides, peptides, antibodies, and biologics. The terms peptides, proteins, and polypeptides are used interchangeably herein. Additionally, the term “therapeutic protein” may refer to the endogenous or naturally occurring correlate of a  
15 therapeutic protein. By a polypeptide displaying a “therapeutic activity” or a protein that is “therapeutically active” is meant a polypeptide that possesses one or more known biological and/or therapeutic activities associated with a therapeutic protein such as one or more of the therapeutic proteins described herein or otherwise known in the art. As a non-limiting example, a “therapeutic protein” is a protein that is useful to treat, prevent or  
20 ameliorate a disease, condition or disorder. Such a disease, condition or disorder may be in humans or in a non-human animal, *e.g.*, veterinary use.

As used herein, the term “transformation” refers to the transfer of nucleic acid (*i.e.*, a nucleotide polymer) into a cell. As used herein, the term “genetic transformation” refers to the transfer and incorporation of DNA, especially recombinant DNA, into a cell.

25 As used herein, the term “transformant” refers to a cell, tissue or organism that has undergone transformation.

As used herein, the term “transgene” refers to a nucleic acid that is inserted into an organism, host cell or vector in a manner that ensures its function.

As used herein, the term “transgenic” refers to cells, cell cultures, organisms,  
30 bacteria, fungi, animals, plants, and progeny of any of the preceding, which have received a foreign or modified gene and in particular a gene encoding a modified Tf fusion protein by one of the various methods of transformation, wherein the foreign or modified gene is

from the same or different species than the species of the organism receiving the foreign or modified gene.

“Variants or variant” refers to a polynucleotide or nucleic acid differing from a reference nucleic acid or polypeptide, but retaining essential properties thereof. Generally, variants are overall closely similar, and, in many regions, identical to the reference nucleic acid or polypeptide. As used herein, “variant”, refers to a therapeutic protein portion of a transferrin fusion protein of the invention, differing in sequence from a native therapeutic protein but retaining at least one functional and/or therapeutic property thereof as described elsewhere herein or otherwise known in the art.

As used herein, the term “vector” refers broadly to any plasmid, phagemid or virus encoding an exogenous nucleic acid. The term is also be construed to include non-plasmid, non-phagemid and non-viral compounds which facilitate the transfer of nucleic acid into virions or cells, such as, for example, polylysine compounds and the like. The vector may be a viral vector that is suitable as a delivery vehicle for delivery of the nucleic acid, or mutant thereof, to a cell, or the vector may be a non-viral vector which is suitable for the same purpose. Examples of viral and non-viral vectors for delivery of DNA to cells and tissues are well known in the art and are described, for example, in Ma *et al.* (1997, *Proc. Natl. Acad. Sci. U.S.A.* 94:12744-12746). Examples of viral vectors include, but are not limited to, a recombinant vaccinia virus, a recombinant adenovirus, a recombinant retrovirus, a recombinant adeno-associated virus, a recombinant avian pox virus, and the like (Cranage *et al.*, 1986, *EMBO J.* 5:3057-3063; International Patent Application No. WO94/17810, published August 18, 1994; International Patent Application No. WO94/23744, published October 27, 1994). Examples of non-viral vectors include, but are not limited to, liposomes, polyamine derivatives of DNA, and the like.

As used herein, the term “wild type” refers to a polynucleotide or polypeptide sequence that is naturally occurring.

### **Transferrin and Transferrin Modifications**

Any transferrin may be used to make modified Tf fusion proteins of the invention. Wild-type human Tf (Tf) is a 679 amino acid protein, of approximately 75kDa (not accounting for glycosylation), with two main domains, N (about 330 amino acids) and C (about 340 amino acids), which appear to originate from a gene duplication. See GenBank

accession numbers NM001063, XM002793, M12530, XM039845, XM 039847 and S95936 (www.ncbi.nlm.nih.gov/), all of which are herein incorporated by reference in their entirety, as well as SEQ ID NOS 1, 2 and 3. The two domains have diverged over time but retain a large degree of identity/similarity (Fig. 1).

5           Each of the N and C domains is further divided into two subdomains, N1 and N2, C1 and C2. The function of Tf is to transport iron to the cells of the body. This process is mediated by the Tf receptor (TfR), which is expressed on all cells, particularly actively growing cells. TfR recognizes the iron bound form of Tf (two of which are bound per receptor), endocytosis then occurs whereby the TfR/Tf complex is transported to the  
10       endosome, at which point the localized drop in pH results in release of bound iron and the recycling of the TfR/Tf complex to the cell surface and release of Tf (known as apoTf in its un-iron bound form). Receptor binding is through the C domain of Tf. The two glycosylation sites in the C domain do not appear to be involved in receptor binding as unglycosylated iron bound Tf does bind the receptor.

15           Each Tf molecule can carry two iron atoms. These are complexed in the space between the N1 and N2, C1 and C2 sub domains resulting in a conformational change in the molecule. Tf crosses the blood brain barrier (BBB) via the Tf receptor.

          In human transferrin, the iron binding sites comprise at least of amino acids Asp 63 (Asp 82 of SEQ ID NO: 2 which comprises the native Tf signal sequence); Asp 392 (Asp  
20       411 of SEQ ID NO: 2); Tyr 95 (Tyr 114 of SEQ ID NO: 2); Tyr 426 (Tyr 445 of SEQ ID NO: 2); Tyr 188 (Tyr 207 of SEQ ID NO: 2); Tyr 514 or 517 (Tyr 533 or Tyr 536 SEQ ID NO:2); His 249 (His 268 of SEQ ID NO: 2); His 585 (His 604 of SEQ ID NO: 2), the hinge regions comprises of at least N domain amino acid residues 94-96, 245- 247 and/or 316-318 as well as C domain amino acid residues 425-427, 581-582 and/or 652-658., the  
25       carbonate binding sites comprise at least of amino acids Thr 120 (Thr 139 of SEQ ID NO: 2); Thr 452 (Thr 471 of SEQ ID NO: 2); Arg 124 (Arg 143 of SEQ ID NO: 2); Arg 456 (Arg 475 of SEQ ID NO: 2); Ala 126 (Ala 145 of SEQ ID NO: 2); Ala 458 (Ala 477 of SEQ ID NO: 2); Gly 127 (Gly 146 of SEQ ID NO: 2); Gly 459 (Gly 478 of SEQ ID NO: 2).

30           In one embodiment of the invention, the modified transferrin fusion protein includes a modified human transferrin, although any animal Tf molecule may be used to produce the fusion proteins of the invention, including human Tf variants, cow, pig, sheep, dog, rabbit, rat, mouse, hamster, echnida, platypus, chicken, frog, hornworm, monkey, as

well as other bovine, canine and avian species (see Figure 2 for a representative set of Tf sequences). All of these Tf sequences are readily available in GenBank and other public databases. The human Tf nucleotide sequence is available (see SEQ ID NOS 1, 2 and 3 and the accession numbers described above and available at [www.ncbi.nlm.nih.gov/](http://www.ncbi.nlm.nih.gov/)) and  
5 can be used to make genetic fusions between Tf or a domain of Tf and the therapeutic molecule of choice. Fusions may also be made from related molecules such as lacto transferrin (lactoferrin) GenBank Acc: NM\_\_002343).

Lactoferrin (Lf), a natural defense iron-binding protein, has been found to possess antibacterial, antimycotic, antiviral, antineoplastic and anti-inflammatory activity. The  
10 protein is present in exocrine secretions that are commonly exposed to normal flora: milk, tears, nasal exudate, saliva, bronchial mucus, gastrointestinal fluids, cervico-vaginal mucus and seminal fluid. Additionally, Lf is a major constituent of the secondary specific granules of circulating polymorphonuclear neutrophils (PMNs). The apoprotein is released on degranulation of the PMNs in septic areas. A principal function of Lf is that  
15 of scavenging free iron in fluids and inflamed areas so as to suppress free radical-mediated damage and decrease the availability of the metal to invading microbial and neoplastic cells. In a study that examined the turnover rate of <sup>125</sup>I Lf in adults, it was shown that LF is rapidly taken up by the liver and spleen, and the radioactivity persisted for several weeks in the liver and spleen (Bennett *et al.* (1979), *Clin. Sci. (Lond.)* 57: 453-460).

20 In another embodiment, the transferrin portion of the transferrin fusion protein of the invention includes a transferrin splice variant. In one example, a transferrin splice variant can be a splice variant of human transferrin. In one specific embodiment, the human transferrin splice variant can be that of Genbank Accession AAA61140.

In another embodiment, the transferrin portion of the transferrin fusion protein of the  
25 invention includes a lactoferrin splice variant. In one example, a human serum lactoferrin splice variant can be a novel splice variant of a neutrophil lactoferrin. In one specific embodiment, the neutrophil lactoferrin splice variant can be that of Genbank Accession AAA59479. In another specific embodiment, the neutrophil lactoferrin splice variant can comprise the following amino acid sequence EDCIALKGEDA (SEQ ID NO: 8), which  
30 includes the novel region of splice-variance.

Modified Tf fusions may be made with any Tf protein, fragment, domain, or engineered domain. For instance, fusion proteins may be produced using the full-length Tf sequence, with or without the native Tf signal sequence. Tf fusion proteins may also be



made using a single Tf domain, such as an individual N or C domain. In some embodiments, the use of a single N domain is advantageous as the Tf glycosylation sites reside in the C domain and the N domain, on its own, does not bind iron or the Tf receptor. In other embodiments, fusions of a therapeutic protein to a single C domain may be produced, wherein the C domain is altered to reduce, inhibit or prevent glycosylation, iron binding and/or Tf receptor binding.

In some embodiments, the Tf or Tf portion will be of sufficient length to increase the serum, *in vitro* solution stability or bioavailability of the therapeutic protein compared to the serum stability (half-life), *in vitro* stability or bioavailability of the therapeutic protein in an unfused state. Such an increase in stability, serum half-life or bioavailability may be about a 30%, 50%, 70%, 80%, 90% or more increase over the unfused therapeutic protein. In some cases, the modified transferrin fusion proteins exhibit a serum half-life of about 10-20 or more days, about 12-18 days or about 14-17 days.

When the C domain of Tf is part of the fusion protein, the two N-linked glycosylation sites, amino acid residues corresponding to N413 and N611 of SEQ ID NO:3 may be mutated for expression in a yeast system to prevent glycosylation or hypermannosylation and extend the serum half-life of the fusion protein and/or therapeutic protein (to produce asialo-, or in some instances, monosialo-Tf or disialo-Tf). In addition to Tf amino acids corresponding to N413 and N611, mutations may be to the adjacent residues within the N-X-S/T glycosylation site to prevent or substantially reduce glycosylation. See U.S. Patent 5,986,067 of Funk *et al.* It has also been reported that the N domain of Tf expressed in *Pichia pastoris* becomes O-linked glycosylated with a single hexose at S32 which also may be mutated or modified to prevent such glycosylation.

Accordingly, in one embodiment of the invention, the transferrin fusion protein includes a modified transferrin molecule wherein the transferrin exhibits reduced glycosylation, including but not limited to asialo- monosialo- and disialo- forms of Tf. In another embodiment, the transferrin portion of the transferrin fusion protein includes a recombinant transferrin mutant that is mutated to prevent glycosylation. In another embodiment, the transferrin portion of the transferrin fusion protein includes a recombinant transferrin mutant that is fully glycosylated. In a further embodiment, the transferrin portion of the transferrin fusion protein includes a recombinant human serum transferrin mutant that is mutated to prevent glycosylation, wherein at least one of Asn413 and Asn611 of SEQ ID NO:3 are mutated to an amino acid which does not allow

glycosylation. In another embodiment, the transferrin portion of the transferrin fusion protein includes a recombinant human serum transferrin mutant that is mutated to prevent or substantially reduce glycosylation, wherein mutations may be to the adjacent residues within the N-X-S/T glycosylation site

5 As discussed below in more detail, modified Tf fusion proteins of the invention may also be engineered to not bind iron and/or not bind the Tf receptor. In other embodiments of the invention, the iron binding is retained and the iron binding ability of Tf may be used in two ways, one to deliver a therapeutic protein or peptide(s) to the inside of a cell and/or across the BBB. These embodiments that bind iron and/or the Tf receptor  
10 will often be engineered to reduce or prevent glycosylation to extend the serum half-life of the therapeutic protein. The N domain alone will not bind to TfR when loaded with iron, and the iron bound C domain will bind TfR but not with the same affinity as the whole molecule.

In another embodiment, the transferrin portion of the transferrin fusion protein  
15 includes a recombinant transferrin mutant having a mutation wherein the mutant does not retain the ability to bind metal. In an alternate embodiment, the transferrin portion of the transferrin fusion protein includes a recombinant transferrin mutant having a mutation wherein the mutant has a weaker binding avidity for metal than wild-type serum transferrin. In an alternate embodiment, the transferrin portion of the transferrin fusion  
20 protein includes a recombinant transferrin mutant having a mutation wherein the mutant has a stronger binding avidity for metal than wild-type serum transferrin.

In another embodiment, the transferrin portion of the transferrin fusion protein includes a recombinant transferrin mutant having a mutation wherein the mutant does not retain the ability to bind to the transferrin receptor. In an alternate embodiment, the  
25 transferrin portion of the transferrin fusion protein includes a recombinant transferrin mutant having a mutation wherein the mutant has a weaker binding avidity for the transferrin receptor than wild-type serum transferrin. In an alternate embodiment, the transferrin portion of the transferrin fusion protein includes a recombinant transferrin mutant having a mutation wherein the mutant has a stronger binding avidity for the  
30 transferrin receptor than wild-type serum transferrin.

In another embodiment, the transferrin portion of the transferrin fusion protein includes a recombinant transferrin mutant having a mutation wherein the mutant does not retain the ability to bind to carbonate. In an alternate embodiment, the transferrin portion

of the transferrin fusion protein includes a recombinant transferrin mutant having a mutation wherein the mutant has a weaker binding avidity for carbonate than wild-type serum transferrin. In an alternate embodiment, the transferrin portion of the transferrin fusion protein includes a recombinant transferrin mutant having a mutation wherein the mutant has a stronger binding avidity for carbonate than wild-type serum transferrin.

In another embodiment, the transferrin portion of the transferrin fusion protein includes a recombinant human serum transferrin mutant having a mutation in at least one amino acid residue selected from the group consisting of Asp63, Gly65, Tyr95, Tyr188, His249, Asp392, Tyr426, Tyr514, Tyr517 and His585 of SEQ ID NO:3, wherein the mutant retains the ability to bind metal. In an alternate embodiment, a recombinant human serum transferrin mutant having a mutation in at least one amino acid residue selected from the group consisting of Asp63, Gly65, Tyr95, Tyr188, His249, Asp392, Tyr426, Tyr514, Tyr517 and His585 of SEQ ID NO:3, wherein the mutant has a reduced ability to bind metal. In another embodiment, a recombinant human serum transferrin mutant having a mutation in at least one amino acid residue selected from the group consisting of Asp63, Gly65, Tyr95, Tyr188, His249, Asp392, Tyr426, Tyr517 and His585 of SEQ ID NO:3, wherein the mutant does not retain the ability to bind metal.

In another embodiment, the transferrin portion of the transferrin fusion protein includes a recombinant human serum transferrin mutant having a mutation at Lys206 or His207 of SEQ ID NO:3, wherein the mutant has a stronger binding avidity for metal than wild-type human serum transferrin (see U.S. Patent 5,986,067, which is herein incorporated by reference in its entirety). In an alternate embodiment, the transferrin portion of the transferrin fusion protein includes a recombinant human serum transferrin mutant having a mutation at Lys206 or His207 of SEQ ID NO:3, wherein the mutant has a weaker binding avidity for metal than wild-type human serum transferrin. In a further embodiment, the transferrin portion of the transferrin fusion protein includes a recombinant human serum transferrin mutant having a mutation at Lys206 or His207 of SEQ ID NO:3, wherein the mutant does not bind metal.

Any available technique may be used to make the fusion proteins of the invention, including but not limited to molecular techniques commonly available, for instance, those disclosed in Sambrook *et al.* Molecular Cloning: A Laboratory Manual, 2nd Ed., Cold Spring Harbor Laboratory Press, 1989. When carrying out nucleotide substitutions using techniques for accomplishing site-specific mutagenesis that are well known in the art, the

encoded amino acid changes are preferably of a minor nature, that is, conservative amino acid substitutions, although other, non-conservative, substitutions are contemplated as well, particularly when producing a modified transferrin portion of a Tf fusion protein, *e.g.*, a modified Tf fusion protein exhibiting reduced glycosylation, reduced iron binding and the like. Specifically contemplated are amino acid substitutions, small deletions or insertions, typically of one to about 30 amino acids; insertions between transferrin domains; small amino- or carboxyl-terminal extensions, such as an amino-terminal methionine residue, or small linker peptides of less than 50, 40, 30, 20 or 10 residues between transferrin domains or linking a transferrin protein and a therapeutic protein or peptide; or a small extension that facilitates purification, such as a poly-histidine tract, an antigenic epitope or a binding domain.

Examples of conservative amino acid substitutions are substitutions made within the same group such as within the group of basic amino acids (such as arginine, lysine, histidine), acidic amino acids (such as glutamic acid and aspartic acid), polar amino acids (such as glutamine and asparagine), hydrophobic amino acids (such as leucine, isoleucine, valine), aromatic amino acids (such as phenylalanine, tryptophan, tyrosine) and small amino acids (such as glycine, alanine, serine, threonine, methionine).

Non-conservative substitutions encompass substitutions of amino acids in one group by amino acids in another group. For example, a non-conservative substitution would include the substitution of a polar amino acid for a hydrophobic amino acid. For a general description of nucleotide substitution, see *e.g.* Ford *et al.* (1991), *Prot. Exp. Pur.* 2: 95-107. Non-conservative substitutions, deletions and insertions are particularly useful to produce TF fusion proteins of the invention that exhibit no or reduced binding of iron, no or reduced binding of the fusion protein to the Tf receptor and/or no or reduced glycosylation.

In the polypeptide and proteins of the invention, the following system is followed for designating amino acids in accordance with the following conventional list:

TABLE OF AMINO ACIDS

AMINO ACID	ONE- LETTER SYMBOL	THREE-LETTER SYMBOL
Alanine	A	Ala
Arginine	R	Arg
Asparagine	N	Asn

AMINO ACID	ONE- LETTER SYMBOL	THREE-LETTER SYMBOL
Aspartic Acid	D	Asp
Cysteine	C	Cys
Glutamine	Q	Gln
Glutamic Acid	E	Glu
Glycine	G	Gly
Histidine	H	His
Isoleucine	I	Ile
Leucine	L	Leu
Lysine	K	Lys
Methionine	M	Met
Phenylalanine	F	Phe
Proline	P	Pro
Serine	S	Ser
Threonine	T	Thr
Tryptophan	W	Trp
Tyrosine	Y	Tyr
Valine	V	Val

Iron binding and/or receptor binding may be reduced or disrupted by mutation, including deletion, substitution or insertion into, amino acid residues corresponding to one or more of Tf N domain residues Asp63, Tyr95, Tyr188, His249 and/or C domain residues Asp 392, Tyr 426, Tyr 514 and/or His 585. Iron binding may also be affected by mutation to amino acids Lys206, Hys207 or Arg632. Carbonate binding may be reduced or disrupted by mutation, including deletion, substitution or insertion into, amino acid residues corresponding to one or more of Tf N domain residues Thr120, Arg124, Ala126, Gly 127 and/or C domain residues Thr 452, Arg 456, Ala 458 and/or Gly 459. A reduction or disruption of carbonate binding may adversely affect iron and/or receptor binding.

Binding to the Tf receptor may be reduced or disrupted by mutation, including deletion, substitution or insertion into, amino acid residues corresponding to one or more of Tf N domain residues described above for iron binding.

As discussed above, glycosylation may be reduced or prevented by mutation, including deletion, substitution or insertion into, amino acid residues corresponding to one or more of Tf C domain residues around the N-X-S/T sites corresponding to C domain residues N413 and/or N611 (See U.S. Patent No. 5,986,067). For instance, the N413 and/or N611 may be mutated to Glu residues.

In instances where the Tf fusion proteins of the invention are not modified to prevent glycosylation, iron binding, carbonate binding and/or receptor binding, glycosylation, iron and/or carbonate ions may be stripped from or cleaved off of the fusion protein. For instance, available de-glycosylases may be used to cleave glycosylation  
5 residues from the fusion protein, in particular the sugar residues attached to the Tf portion, yeast deficient in glycosylation enzymes may be used to prevent glycosylation and/or recombinant cells may be grown in the presence of an agent that prevents glycosylation, *e.g.*, tunicamycin.

Additional mutations may be made with Tf to alter the three dimensional structure  
10 of TF, such as modifications to the hinge region to prevent Tf folding needed for iron binding and Tf receptor recognition. For instance, mutations may be made in or around N domain amino acid residues 94-96, 245-247 and/or 316-318 as well as C domain amino acid residues 425-427, 581-582 and/or 652-658. In addition, mutations may be made in to or around the flanking regions of these sites to alter Tf structure and function.

15 In one aspect of the invention, the transferrin fusion protein can function as a carrier protein to extend the half life or bioavailability of the therapeutic protein as well as in some instances, delivering the therapeutic protein inside a cell and/or across the blood brain barrier. In an alternate embodiment, the transferrin fusion protein includes a modified transferrin molecule wherein the transferrin does not retain the ability to cross  
20 the blood brain barrier.

In another embodiment, the transferrin fusion protein includes a modified transferrin molecule wherein the transferrin molecule retains the ability to bind to the transferrin receptor and transport the therapeutic peptide inside cells. In an alternate  
25 embodiment, the transferrin fusion protein includes a modified transferrin molecule wherein the transferrin molecule does not retain the ability to bind to the transferrin receptor and transport the therapeutic peptide inside cells.

In further embodiments, the transferrin fusion protein includes a modified transferrin molecule wherein the transferrin molecule retains the ability to bind to the transferrin receptor and transport the therapeutic peptide inside cells, but does not retain  
30 the ability to cross the blood brain barrier. In an alternate embodiment, the transferrin fusion protein includes a modified transferrin molecule wherein the transferrin molecule retains the ability to cross the blood brain barrier, but does not retain the ability to bind to the transferrin receptor and transport the therapeutic peptide inside cells.

### Modified Transferrin Fusion Proteins

The fusion of proteins of the invention may contain one or more copies of the therapeutic protein attached to the N-terminus and/or the C-terminus of the Tf protein. In some embodiments, the therapeutic protein is attached to both the N- and C-terminus of the Tf protein and the fusion protein may contain one or more equivalents of the therapeutic protein on either or both ends of Tf. In other embodiments, the therapeutic protein or polypeptide is inserted into known domains of the Tf protein, for instance, into one or more of the loops of Tf (see Ali *et al.* (1999) *J. Biolog. Chem.* 274(34):24066-24073). In other embodiments, the therapeutic protein or therapeutic peptide is inserted between the N and C domains of Tf.

Generally, the transferrin fusion protein of the inventions of the invention may have one modified transferrin-derived region and one therapeutic protein-derived region. Multiple regions of each protein, however, may be used to make a transferrin fusion protein of the invention. Similarly, more than one therapeutic protein may be used to make a transferrin fusion protein of the invention of the invention, thereby producing a multi-functional modified Tf fusion protein.

In one embodiment, the transferrin fusion protein of the invention contains a therapeutic protein or portion thereof fused to a transferrin molecule or portion thereof. In another embodiment, the transferrin fusion protein of the inventions contains a therapeutic protein fused to the N terminus of a transferrin molecule. In an alternate embodiment, the transferrin fusion protein of the invention contains a therapeutic protein fused to the C terminus of a transferrin molecule. In a further embodiment, the transferrin fusion protein of the invention contains a transferrin molecule fused to the N terminus of a therapeutic protein. In an alternate embodiment, the transferrin fusion protein of the invention contains a transferrin molecule fused to the C terminus of a therapeutic protein.

In further embodiments, the modified transferrin molecule contains the N terminus of a transferrin molecule fused to what would be the N terminus of a therapeutic peptide. In an alternate embodiment, the modified transferrin molecule contains the N terminus of a transferrin molecule fused to the C terminus of a therapeutic peptide. In a further alternate embodiment, the modified transferrin molecule contains the C terminus of a transferrin molecule fused to what would be the C terminus of a therapeutic peptide. In an

alternate embodiment, the modified transferrin molecule contains the C terminus of a transferrin molecule fused to the N terminus of a therapeutic peptide.

In other embodiments, the transferrin fusion protein of the inventions contains a therapeutic protein fused to both the N-terminus and the C-terminus of modified  
5 transferrin. In another embodiment, the therapeutic proteins fused at the N- and C- termini are the same therapeutic proteins. In an alternate embodiment, the therapeutic proteins fused at the N- and C- termini are different therapeutic proteins. In another alternate  
10 embodiment, the therapeutic proteins fused to the N- and C- termini are different therapeutic proteins which may be used to treat or prevent the same disease, disorder, or condition. In another embodiment, the therapeutic proteins fused at the N- and C- termini are different therapeutic proteins which may be used to treat or prevent diseases or disorders which are known in the art to commonly occur in patients simultaneously.

In addition to modified transferrin fusion protein of the inventions in which the modified transferrin portion is fused to the N terminal and/or C-terminal of the therapeutic  
15 protein portion, transferrin fusion protein of the inventions of the invention may also be produced by inserting the therapeutic protein or peptide of interest (*e.g.*, a therapeutic protein or peptide as disclosed herein, or, for instance, a single chain antibody that binds a therapeutic protein or a fragment or variant thereof) into an internal region of the modified  
20 transferrin. Internal regions of modified transferrin include, but are not limited to, the iron binding sites, the hinge regions, the bicarbonate binding sites, or the receptor binding domain.

Within the protein sequence of the modified transferrin molecule a number of loops or turns exist, which are stabilized by disulfide bonds. These loops are useful for the  
25 insertion, or internal fusion, of therapeutically active peptides, particularly those requiring a secondary structure to be functional, or therapeutic proteins, to essentially generate a modified transferrin molecule with specific biological activity.

When therapeutic proteins or peptides are inserted into or replace at least one loop of a Tf molecule, insertions may be made within any of the surface exposed loop regions, in addition to other areas of Tf. For instance, insertions may be made within the loops  
30 comprising TF amino acids 32-33, 74-75, 256-257, 279-280 and 288-289 (Ali *et al.*, *supra*) (See Figure 3). As previously described, insertions may also be made within other regions of Tf such as the sites for iron and bicarbonate binding, hinge regions, and the receptor binding domain as described in more detail below. The loops in the Tf protein



sequence that are amenable to modification/replacement for the insertion of proteins or peptides may also be used for the development of a screenable library of random peptide inserts. Any procedures may be used to produce nucleic acid inserts for the generation of peptide libraries, including available phage and bacterial display systems, prior to cloning into a Tf domain and/or fusion to the ends of Tf.

The N-terminus of Tf is free and points away from the body of the molecule. Fusions of proteins or peptides on the N-terminus may therefore be a preferred embodiment. Such fusions may include a linker region, such as but not limited to a poly-glycine stretch, to separate the therapeutic protein or peptide from Tf. Attention to the junction between the leader sequence, the choice of leader sequence, and the structure of the mRNA by codon manipulation/optimization (no major stem loops to inhibit ribosome progress) will increase secretion and can be readily accomplished using standard recombinant protein techniques.

The C-terminus of Tf appears to be more buried and secured by a disulfide bond 6 amino acids from the C-terminus. In human Tf, the C-terminal amino acid is a proline which, depending on the way that it is orientated, will either point a fusion away or into the body of the molecule. A linker or spacer moiety at the C-terminus may be used in some embodiments of the invention.

In yet other embodiments, small molecule therapeutics may be complexed with iron and loaded on a modified Tf protein fusion for delivery to the inside of cells and across the BBB. The addition of a targeting peptide or, for example, a SCA will target the payload to a particular cell type, *e.g.*, a cancer cell.

### **Nucleic Acids**

Nucleic acid molecules are also provided by the present invention. These encode a modified Tf fusion protein comprising a transferrin protein or a portion of a transferrin protein covalently linked or joined to a therapeutic protein. As discussed in more detail below, any therapeutic protein may be used. The fusion protein may further comprise a linker region, for instance a linker less than about 50, 40, 30, 20, or 10 amino acid residues. The linker can be covalently linked to and between the transferrin protein or portion thereof and the therapeutic protein. Nucleic acid molecules of the invention may be purified or not.

Host cells and vectors for replicating the nucleic acid molecules and for expressing the encoded fusion proteins are also provided. Any vectors or host cells may be used, whether prokaryotic or eukaryotic, but eukaryotic expression systems, in particular yeast expression systems, may be preferred. Many vectors and host cells are known in the art for such purposes. It is well within the skill of the art to select an appropriate set for the desired application.

DNA sequences encoding transferrin, portions of transferrin and therapeutic proteins of interest may be cloned from a variety of genomic or cDNA libraries known in the art. The techniques for isolating such DNA sequences using probe-based methods are conventional techniques and are well known to those skilled in the art. Probes for isolating such DNA sequences may be based on published DNA or protein sequences (see, for example, Baldwin, G.S. (1993) Comparison of Transferrin Sequences from Different Species. *Comp. Biochem. Physiol.* 106B/1:203-218 and all references cited therein, which are hereby incorporated by reference in their entirety). Alternatively, the polymerase chain reaction (PCR) method disclosed by Mullis *et al.* (U.S. Pat. No. 4,683,195) and Mullis (U.S. Pat. No. 4,683,202), incorporated herein by reference may be used. The choice of library and selection of probes for the isolation of such DNA sequences is within the level of ordinary skill in the art.

As known in the art "similarity" between two polynucleotides or polypeptides is determined by comparing the nucleotide or amino acid sequence and its conserved nucleotide or amino acid substitutes of one polynucleotide or polypeptide to the sequence of a second polynucleotide or polypeptide. Also known in the art is "identity" which means the degree of sequence relatedness between two polypeptide or two polynucleotide sequences as determined by the identity of the match between two strings of such sequences. Both identity and similarity can be readily calculated (Computational Molecular Biology, Lesk, A. M., ed., Oxford University Press, New York, 1988; Biocomputing: Informatics and Genome Projects, Smith, D. W., ed., Academic Press, New York, 1993; Computer Analysis of Sequence Data, Part I, Griffin, A. M., and Griffin, H. G., eds., Humana Press, New Jersey, 1994; Sequence Analysis in Molecular Biology, von Heinje, G., Academic Press, 1987; and Sequence Analysis Primer, Gribskov, M. and Devereux, J., eds., M Stockton Press, New York, 1991).

While there exist a number of methods to measure identity and similarity between two polynucleotide or polypeptide sequences, the terms "identity" and "similarity" are

well known to skilled artisans (Sequence Analysis in Molecular Biology, von Heinje, G., Academic Press, 1987; Sequence Analysis Primer, Gribskov, M. and Devereux, J., eds., M Stockton Press, New York, 1991; and Carillo, H., and Lipman, D., SIAM J. Applied Math., 48: 1073 (1988). Methods commonly employed to determine identity or similarity  
5 between two sequences include, but are not limited to those disclosed in Guide to Huge Computers, Martin J. Bishop, ed., Academic Press, San Diego, 1994, and Carillo, H., and Lipman, D., SIAM J. Applied Math. 48:1073 (1988).

Preferred methods to determine identity are designed to give the largest match between the two sequences tested. Methods to determine identity and similarity are  
10 codified in computer programs. Preferred computer program methods to determine identity and similarity between two sequences include, but are not limited to, GCG program package (Devereux, *et al.*, Nucleic Acids Research 12(1):387 (1984)), BLASTP, BLASTN, FASTA (Atschul, *et al.*, J. Molec. Biol. 215:403 (1990)). The degree of similarity or identity referred to above is determined as the degree of identity between the  
15 two sequences indicating a derivation of the first sequence from the second. The degree of identity between two nucleic acid sequences may be determined by means of computer programs known in the art such as GAP provided in the GCG program package (Needleman and Wunsch (1970) Journal of Molecular Biology 48:443-453). For purposes  
20 of determining the degree of identity between two nucleic acid sequences for the present invention, GAP is used with the following settings: GAP creation penalty of 5.0 and GAP extension penalty of 0.3.

### **Codon Optimization**

The degeneracy of the genetic code permits variations of the nucleotide sequence  
25 of a transferrin protein and/or therapeutic protein of interest, while still producing a polypeptide having the identical amino acid sequence as the polypeptide encoded by the native DNA sequence. The procedure, known as "codon optimization" (described in U.S. Patent 5,547,871 which is incorporated herein by reference in its entirety) provides one with a means of designing such an altered DNA sequence. The design of codon optimized  
30 genes should take into account a variety of factors, including the frequency of codon usage in an organism, nearest neighbor frequencies, RNA stability, the potential for secondary structure formation, the route of synthesis and the intended future DNA manipulations of that gene. In particular, available methods may be used to alter the codons encoding a

given fusion protein with those most readily recognized by yeast when yeast expression systems are used.

The degeneracy of the genetic code permits the same amino acid sequence to be encoded and translated in many different ways. For example, leucine, serine and arginine are each encoded by six different codons, while valine, proline, threonine, alanine and glycine are each encoded by four different codons. However, the frequency of use of such synonymous codons varies from genome to genome among eukaryotes and prokaryotes. For example, synonymous codon-choice patterns among mammals are very similar, while evolutionarily distant organisms such as yeast (*S. cerevisiae*), bacteria (such as *E. coli*) and insects (such as *D. melanogaster*) reveal a clearly different pattern of genomic codon use frequencies (Grantham, R., *et al.*, Nucl. Acids Res., 8, 49-62 (1980); Grantham, R., *et al.*, Nucl. Acids Res., 9, 43-74 (1981); Maruyama, T., *et al.*, Nucl. Acids Res., 14, 151-197 (1986); Aota, S., *et al.*, Nucl. Acids Res., 16, 315-402 (1988); Wada, K., *et al.*, Nucl. Acids Res., 19 Supp., 1981-1985 (1991); Kurland, C. G., FEBS Letters, 285, 165-169 (1991)). These differences in codon-choice patterns appear to contribute to the overall expression levels of individual genes by modulating peptide elongation rates. (Kurland, C. G., FEBS Letters, 285, 165-169 (1991); Pedersen, S., EMBO J., 3, 2895-2898 (1984); Sorensen, M. A., J. Mol. Biol., 207, 365-377 (1989); Randall, L. L., *et al.*, Eur. J. Biochem., 107, 375-379 (1980); Curran, J. F., and Yarus, M., J. Mol. Biol., 209, 65-77 (1989); Varenne, S., *et al.*, J. Mol. Biol., 180, 549-576 (1984); Varenne, S., *et al.*, J. Mol. Biol., 180, 549-576 (1984); Garel, J.-P., J. Theor. Biol., 43, 211-225 (1974); Ikemura, T., J. Mol. Biol., 146, 1-21 (1981); Ikemura, T., J. Mol. Biol., 151, 389-409 (1981)).

The preferred codon usage frequencies for a synthetic gene should reflect the codon usages of nuclear genes derived from the exact (or as closely related as possible) genome of the cell/organism that is intended to be used for recombinant protein expression, particularly that of yeast species. As discussed above, in one preferred embodiment the human Tf sequence is codon optimized, before or after modification as herein described for yeast expression as may be the therapeutic protein nucleotide sequence(s).

### Vectors

Expression units for use in the present invention will generally comprise the following elements, operably linked in a 5' to 3' orientation: a transcriptional promoter, a

secretory signal sequence, a DNA sequence encoding a modified Tf fusion protein comprising transferrin protein or a portion of a transferrin protein joined to a DNA sequence encoding a therapeutic protein or peptide of interest and a transcriptional terminator. As discussed above, any arrangement of the therapeutic protein or peptide fused to or within the Tf portion may be used in the vectors of the invention. The selection of suitable promoters, signal sequences and terminators will be determined by the selected host cell and will be evident to one skilled in the art and are discussed more specifically below.

Suitable yeast vectors for use in the present invention are described in U.S. Patent 6,291,212 and include YRp7 (Struhl *et al.*, Proc. Natl. Acad. Sci. USA 76: 1035-1039, 1978), YEpl3 (Broach *et al.*, Gene 8: 121-133, 1979), pJDB249 and pJDB219 (Beggs, Nature 275:104-108, 1978), pPPC0005, pSeCHSA, pScNHSA, pC4 and derivatives thereof. Useful yeast plasmid vectors also include pRS403-406, pRS413-416 and the *Pichia* vectors available from Stratagene Cloning Systems, La Jolla, CA 92037, USA. Plasmids pRS403, pRS404, pRS405 and pRS406 are Yeast Integrating plasmids (YIps) and incorporate the yeast selectable markers HIS3, 7RPI, LEU2 and URA3. Plasmids pRS413-416 are Yeast Centromere plasmids (Ycps).

Such vectors will generally include a selectable marker, which may be one of any number of genes that exhibit a dominant phenotype for which a phenotypic assay exists to enable transformants to be selected. Preferred selectable markers are those that complement host cell auxotrophy, provide antibiotic resistance or enable a cell to utilize specific carbon sources, and include LEU2 (Broach *et al.* *ibid.*), URA3 (Botstein *et al.*, Gene 8: 17, 1979), HIS3 (Struhl *et al.*, *ibid.*) or POT1 (Kawasaki and Bell, EP 171,142). Other suitable selectable markers include the CAT gene, which confers chloramphenicol resistance on yeast cells. Preferred promoters for use in yeast include promoters from yeast glycolytic genes (Hitzeman *et al.*, J Biol. Chem. 225: 12073-12080, 1980; Alber and Kawasaki, J. Mol. Appl. Genet. 1: 419-434, 1982; Kawasaki, U.S. Pat. No. 4,599,311) or alcohol dehydrogenase genes (Young *et al.*, in Genetic Engineering of Microorganisms for Chemicals, Hollaender *et al.*, (eds.), p. 355, Plenum, N.Y., 1982; Ammerer, Meth. Enzymol. 101: 192-201, 1983). In this regard, particularly preferred promoters are the TPI1 promoter (Kawasaki, U.S. Pat. No. 4,599,311) and the ADH2-4.sup.C [see U.S. Patent 6,291,212] promoter (Russell *et al.*, Nature 304: 652-654, 1983). The expression

units may also include a transcriptional terminator. A preferred transcriptional terminator is the TPI1 terminator (Alber and Kawasaki, *ibid.*).

In addition to yeast, modified fusion proteins of the present invention can be expressed in filamentous fungi, for example, strains of the fungi *Aspergillus*. Examples of  
5 useful promoters include those derived from *Aspergillus nidulans* glycolytic genes, such as the ADH3 promoter (McKnight *et al.*, EMBO J. 4: 2093-2099, 1985) and the *tpiA* promoter. An example of a suitable terminator is the ADH3 terminator (McKnight *et al.*, *ibid.*). The expression units utilizing such components may be cloned into vectors that are capable of insertion into the chromosomal DNA of *Aspergillus*, for example.

10 Mammalian expression vectors for use in carrying out the present invention will include a promoter capable of directing the transcription of the modified Tf fusion protein. Preferred promoters include viral promoters and cellular promoters. Preferred viral promoters include the major late promoter from adenovirus 2 (Kaufman and Sharp, Mol. Cell. Biol. 2: 1304-1319, 1982) and the SV40 promoter (Subramani *et al.*, Mol. Cell.  
15 Biol. 1: 854-864, 1981). Preferred cellular promoters include the mouse metallothionein 1 promoter (Palmiter *et al.*, Science 222: 809-814, 1983) and a mouse V.sub..kappa. [see U.S. Patent 6,291,212] promoter (Grant *et al.*, Nuc. Acids Res. 15: 5496, 1987). A particularly preferred promoter is a mouse V.sub.H [see U.S. Patent 6,291,212] promoter (Loh *et al.*, *ibid.*). Such expression vectors may also contain a set of RNA splice sites  
20 located downstream from the promoter and upstream from the DNA sequence encoding the transferrin fusion protein. Preferred RNA splice sites may be obtained from adenovirus and/or immunoglobulin genes.

Also contained in the expression vectors is a polyadenylation signal located downstream of the coding sequence of interest. Polyadenylation signals include the early  
25 or late polyadenylation signals from SV40 (Kaufman and Sharp, *ibid.*), the polyadenylation signal from the adenovirus 5 E1B region and the human growth hormone gene terminator (DeNoto *et al.*, Nuc. Acids Res. 9: 3719-3730, 1981). A particularly preferred polyadenylation signal is the V.sub.H [see U.S. Patent 6,291,212] gene terminator (Loh *et al.*, *ibid.*). The expression vectors may include a noncoding viral leader  
30 sequence, such as the adenovirus 2 tripartite leader, located between the promoter and the RNA splice sites. Preferred vectors may also include enhancer sequences, such as the SV40 enhancer and the mouse .mu. [see U.S. Patent 6,291,212] enhancer (Gillies, Cell 33:

717-728, 1983). Expression vectors may also include sequences encoding the adenovirus VA RNAs.

### Transformation

5 Techniques for transforming fungi are well known in the literature, and have been described, for instance, by Beggs (*ibid.*), Hinnen *et al.* (Proc. Natl. Acad. Sci. USA 75: 1929-1933, 1978), Yelton *et al.*, (Proc. Natl. Acad. Sci. USA 81: 1740-1747, 1984), and Russell (Nature 301: 167-169, 1983). The genotype of the host cell will generally contain a genetic defect that is complemented by the selectable marker present on the expression  
10 vector. Choice of a particular host and selectable marker is well within the level of ordinary skill in the art.

Cloned DNA sequences comprising modified Tf fusion proteins of the invention may be introduced into cultured mammalian cells by, for example, calcium phosphate-mediated transfection (Wigler *et al.*, Cell 14: 725, 1978; Corsaro and Pearson, Somatic  
15 Cell Genetics 7: 603, 1981; Graham and Van der Eb, Virology 52: 456, 1973.) Other techniques for introducing cloned DNA sequences into mammalian cells, such as electroporation (Neumann *et al.*, EMBO J. 1: 841-845, 1982), or lipofection may also be used. In order to identify cells that have integrated the cloned DNA, a selectable marker is generally introduced into the cells along with the gene or cDNA of interest. Preferred  
20 selectable markers for use in cultured mammalian cells include genes that confer resistance to drugs, such as neomycin, hygromycin, and methotrexate. The selectable marker may be an amplifiable selectable marker. A preferred amplifiable selectable marker is the DHFR gene. A particularly preferred amplifiable marker is the DHFR.sup.r [see U.S. Patent 6,291,212] cDNA (Simonsen and Levinson, Proc. Natl. Acad. Sci. USA  
25 80: 2495-2499, 1983). Selectable markers are reviewed by Thilly (Mammalian Cell Technology, Butterworth Publishers, Stoneham, Mass.) and the choice of selectable markers is well within the level of ordinary skill in the art.

### Host Cells

30 The present invention also includes a cell, preferably a yeast cell transformed to express a modified transferrin fusion protein of the invention. In addition to the transformed host cells themselves, the present invention also includes a culture of those cells, preferably a monoclonal (clonally homogeneous) culture, or a culture derived from a

monoclonal culture, in a nutrient medium. If the polypeptide is secreted, the medium will contain the polypeptide, with the cells, or without the cells if they have been filtered or centrifuged away.

Host cells for use in practicing the present invention include eukaryotic cells, and in some cases prokaryotic cells, capable of being transformed or transfected with exogenous DNA and grown in culture, such as cultured mammalian, insect, fungal, plant and bacterial cells.

Fungal cells, including species of yeast (e.g., *Saccharomyces* spp., *Schizosaccharomyces* spp., *Pichia* spp.) may be used as host cells within the present invention. Exemplary genera of yeast contemplated to be useful in the practice, of the present invention as hosts for expressing the, transferrin fusion protein of the inventions are *Pichia* (formerly classified as *Hansenula*), *Saccharomyces*, *Kluyveromyces*, *Aspergillus*, *Candida*, *Torulopsis*, *Torulaspora*, *Schizosaccharomyces*, *Citeromyces*, *Pachysolen*, *Zygosaecharomyces*, *Debaromyces*, *Trichoderma*, *Cephalosporium*, *Humicola*, *Mucor*, *Neurospora*, *Yarrowia*, *Metschnikowia*, *Rhodospiridium*, *Leucosporidium*, *Botryosascus*, *Sporidiobolus*, *Endomycopsis*, and the like. Examples of *Saccharomyces* spp. are *S. cerevisiae*, *S. italicus* and *S. rouxii*. Examples of *Kluyveromyces* spp. are *K. fragilis*, *K. lactis* and *K. marxianus*. A suitable *Torulaspora* species is *T. delbrueckii*. Examples of *Pichia* (*Hansenula*) spp. are *P. angusta* (formerly *H. polymorpha*), *P. anomala* (formerly *H. anomala*) and *P. pastoris*.

Particularly useful host cells to produce the Tf fusion proteins of the invention are the methanotrophic *Pichia pastoris* (Steinlein *et al.* (1995) *Protein Express. Purif.* 6:619-624). *Pichia pastoris* has been developed to be an outstanding host for the production of foreign proteins since its alcohol oxidase promoter was isolated and cloned; its transformation was first reported in 1985. *P. pastoris* can utilize methanol as a carbon source in the absence of glucose. The *P. pastoris* expression system can use the methanol-induced alcohol oxidase (AOX1) promoter, which controls the gene that codes for the expression of alcohol oxidase, the enzyme which catalyzes the first step in the metabolism of methanol. This promoter has been characterized and incorporated into a series of *P. pastoris* expression vectors. Since the proteins produced in *P. pastoris* are typically folded correctly and secreted into the medium, the fermentation of genetically engineered *P. pastoris* provides an excellent alternative to *E. coli* expression systems. A number of



proteins have been produced using this system, including tetanus toxin fragment, Bordatella pertussis pertactin, human serum albumin and lysozyme.

The transformation of *F. oxysporum* may, for instance, be carried out as described by Malardier *et al.* (1989) Gene 78:147-156.

5        Strains of the yeast *Saccharomyces cerevisiae* are another preferred host. In a preferred embodiment, a yeast cell, or more specifically, a *Saccharomyces cerevisiae* host cell that contains a genetic deficiency in a gene required for asparagine-linked glycosylation of glycoproteins is used. *S. cerevisiae* host cells having such defects may be prepared using standard techniques of mutation and selection, although many available  
10       yeast strains have been modified to prevent or reduce glycosylation or hypermannosylation. Ballou *et al.* (J. Biol. Chem. 255: 5986-5991, 1980) have described the isolation of mannoprotein biosynthesis mutants that are defective in genes which affect asparagine-linked glycosylation.

To optimize production of the heterologous proteins, it is also preferred that the  
15       host strain carries a mutation, such as the *S. cerevisiae* pep4 mutation (Jones, Genetics 85: 23-33, 1977), which results in reduced proteolytic activity. Host strains containing mutations in other protease encoding regions are particularly useful to produce large quantities of the Tf fusion proteins of the invention.

Host cells containing DNA constructs of the present invention are grown in an  
20       appropriate growth medium. As used herein, the term "appropriate growth medium" means a medium containing nutrients required for the growth of cells. Nutrients required for cell growth may include a carbon source, a nitrogen source, essential amino acids, vitamins, minerals and growth factors. The growth medium will generally select for cells containing the DNA construct by, for example, drug selection or deficiency in an essential  
25       nutrient which are complemented by the selectable marker on the DNA construct or co-transfected with the DNA construct. Yeast cells, for example, are preferably grown in a chemically defined medium, comprising a non-amino acid nitrogen source, inorganic salts, vitamins and essential amino acid supplements. The pH of the medium is preferably maintained at a pH greater than 2 and less than 8, preferably at pH 6.5. Methods for  
30       maintaining a stable pH include buffering and constant pH control, preferably through the addition of sodium hydroxide. Preferred buffering agents include succinic acid and Bis-Tris (Sigma Chemical Co., St. Louis, Mo.). Yeast cells having a defect in a gene required for asparagine-linked glycosylation are preferably grown in a medium containing an

osmotic stabilizer. A preferred osmotic stabilizer is sorbitol supplemented into the medium at a concentration between 0.1 M and 1.5 M., preferably at 0.5 M or 1.0 M.

Cultured mammalian cells are generally grown in commercially available serum-containing or serum-free media. Selection of a medium appropriate for the particular cell line used is within the level of ordinary skill in the art. Transfected mammalian cells are allowed to grow for a period of time, typically 1-2 days, to begin expressing the DNA sequence(s) of interest. Drug selection is then applied to select for growth of cells that are expressing the selectable marker in a stable fashion. For cells that have been transfected with an amplifiable selectable marker the drug concentration may be increased in a stepwise manner to select for increased copy number of the cloned sequences, thereby increasing expression levels.

Baculovirus/insect cell expression systems may also be used to produce the modified Tf fusion proteins of the invention. The BacPAK™ Baculovirus Expression System (BD Biosciences (Clontech)) expresses recombinant proteins at high levels in insect host cells. The target gene is inserted into a transfer vector, which is cotransfected into insect host cells with the linearized BacPAK6 viral DNA. The BacPAK6 DNA is missing an essential portion of the baculovirus genome. When the DNA recombines with the vector, the essential element is restored and the target gene is transferred to the baculovirus genome. Following recombination, a few viral plaques are picked and purified, and the recombinant phenotype is verified. The newly isolated recombinant virus can then be amplified and used to infect insect cell cultures to produce large amounts of the desired protein.

### **Secretory Signal Sequences**

The terms "secretory signal sequence" or "signal sequence" or "secretion leader sequence" are used interchangeably and are described, for example in U.S. Pat. 6,291,212 and U.S. Pat 5,547,871, both of which are herein incorporated by reference in their entirety. Secretory signal sequences or signal sequences or secretion leader sequences encode secretory peptides. A secretory peptide is an amino acid sequence that acts to direct the secretion of a mature polypeptide or protein from a cell. Secretory peptides are generally characterized by a core of hydrophobic amino acids and are typically (but not exclusively) found at the amino termini of newly synthesized proteins. Very often the secretory peptide is cleaved from the mature protein during secretion. Secretory peptides

may contain processing sites that allow cleavage of the signal peptide from the mature protein as it passes through the secretory pathway. Processing sites may be encoded within the signal peptide or may be added to the signal peptide by, for example, *in vitro* mutagenesis.

5           Secretory peptides may be used to direct the secretion of modified Tf fusion proteins of the invention. One such secretory peptide that may be used in combination with other secretory peptides is the third domain of the yeast Barrier protein. Secretory signal sequences or signal sequences or secretion leader sequences are required for a complex series of post-translational processing steps which result in secretion of a protein.

10   If an intact signal sequence is present, the protein being expressed enters the lumen of the rough endoplasmic reticulum and is then transported through the Golgi apparatus to secretory vesicles and is finally transported out of the cell. Generally, the signal sequence immediately follows the initiation codon and encodes a signal peptide at the amino-terminal end of the protein to be secreted. In most cases, the signal sequence is cleaved

15   off by a specific protease, called a signal peptidase. Preferred signal sequences improve the processing and export efficiency of recombinant protein expression using viral, mammalian or yeast expression vectors. In some cases, the native Tf signal sequence may be used to express and secrete fusion proteins of the invention.

## 20           **Linkers**

The Tf moiety and therapeutic protein moiety(s) of the modified transferrin fusion proteins of the invention can be fused directly or using a linker peptide of various lengths to provide greater physical separation and allow more spatial mobility between the fused proteins and thus maximize the accessibility of the therapeutic protein portion, for

25   instance, for binding to its cognate receptor. The linker peptide may consist of amino acids that are flexible or more rigid. For example, a linker such as but not limited to a poly-glycine stretch. The linker can be less than about 50, 40, 30, 20, or 10 amino acid residues. The linker can be covalently linked to and between the transferrin protein or portion thereof and the therapeutic protein.

## 30           **Detection of Tf Fusion Proteins**

Assays for detection of biologically active modified transferrin-therapeutic protein fusions may include Western transfer, protein blot or colony filter as well as activity based assays

that detect the fused therapeutic protein. A Western transfer filter may be prepared using the method described by Towbin *et al.* (*Proc. Natl. Acad. Sci. USA* 76: 4350-4354, 1979). Briefly, samples are electrophoresed in a sodium dodecylsulfate polyacrylamide gel. The proteins in the gel are electrophoretically transferred to nitrocellulose paper. Protein blot  
5 filters may be prepared by filtering supernatant samples or concentrates through nitrocellulose filters using, for example, a Minifold (Schleicher & Schuell, Keene, N.H.). Colony filters may be prepared by growing colonies on a nitrocellulose filter that has been laid across an appropriate growth medium. In this method, a solid medium is preferred. The cells are allowed to grow on the filters for at least 12 hours. The cells are removed  
10 from the filters by washing with an appropriate buffer that does not remove the proteins bound to the filters. A preferred buffer comprises 25 mM Tris-base, 19 mM glycine, pH 8.3, 20% methanol.

Fusion proteins of the invention may also be detected by assaying for the activity of the therapeutic protein moiety. Such assays are readily available, including but not  
15 limited to, those assays described in Table 1. Specifically, transferrin fusion proteins of the invention may be assayed for functional activity (*e.g.*, biological activity or therapeutic activity) using the assay referenced in the "Exemplary Activity Assay" column of Table 1. Additionally, one of skill in the art may routinely assay fragments of a therapeutic protein corresponding to a therapeutic protein portion of a fusion protein of the invention, for  
20 activity using assays referenced in its corresponding row of Table 1. Further, one of skill in the art may routinely assay fragments of a modified transferrin protein for activity using assays known in the art.

For example, in one embodiment where one is assaying for the ability of a transferrin fusion protein of the invention to bind or compete with a therapeutic protein for  
25 binding to an anti-therapeutic polypeptide antibody and/or anti-transferrin antibody, various immunoassays known in the art can be, used, including but not limited to, competitive and non-competitive assay systems using techniques such as radioimmunoassays, ELISA (enzyme linked immunosorbent assay), sandwich immunoassays, immunoradiometric assays, gel diffusion precipitation reactions,  
30 immunodiffusion assays, *in situ* immunoassays (using colloidal gold, enzyme or radioisotope labels, for example), western blots, precipitation reactions, agglutination assays (*e.g.*, gel agglutination assays), complement fixation assays, immunofluorescence assays, protein A assays, and immunoelectrophoresis assays, etc. In one embodiment,

antibody binding is detected by detecting a label on the primary antibody. In another embodiment, the primary antibody is detected by detecting binding of a secondary antibody or reagent to the primary antibody. In a further embodiment, the secondary antibody is labeled. Many means are known in the art for detecting binding in an immunoassay and are within the scope of the present invention.

In a further embodiment, where a binding partner (*e.g.*, a receptor or a ligand) of a therapeutic protein is identified, binding to that binding partner by a transferrin fusion protein containing that therapeutic protein as the therapeutic protein portion of the fusion can be assayed, *e.g.*, by means well-known in the art, such as, for example, reducing and non-reducing gel chromatography, protein affinity chromatography, and affinity blotting. Other methods will be known to the skilled artisan and are within the scope of the invention.

#### **Isolation/Purification of Modified Transferrin Fusion Proteins**

Secreted, biologically active, modified transferrin fusion proteins may be isolated from the medium of host cells grown under conditions that allow the secretion of the biologically active fusion proteins. The cell material is removed from the culture medium, and the biologically active fusion proteins are isolated using isolation techniques known in the art. Suitable isolation techniques include precipitation and fractionation by a variety of chromatographic methods, including gel filtration, ion exchange chromatography and affinity chromatography.

A particularly preferred purification method is affinity chromatography on an iron binding or metal chelating column or an immunoaffinity chromatography using an antibody directed against the transferrin or therapeutic protein or peptide portion of the polypeptide fusion. The antibody is preferably immobilized or attached to a solid support or substrate. A particularly preferred substrate is CNBr-activated Sepharose (Pharmacia LKB Technologies, Inc., Piscataway, N.J.). By this method, the medium is combined with the antibody/substrate under conditions that will allow binding to occur. The complex may be washed to remove unbound material, and the transferrin fusion protein is released or eluted through the use of conditions unfavorable to complex formation. Particularly useful methods of elution include changes in pH, wherein the immobilized antibody has a high affinity for the ligand at a first pH and a reduced affinity at a second (higher or lower)

pH; changes in concentration of certain chaotropic agents; or through the use of detergents.

### **Labeled Modified Transferrin Fusion Proteins**

5 Transferrin fusion proteins of the present invention may also be labeled with a radioisotope or other imaging agent and used for *in vivo* diagnostic purposes. Preferred radioisotope imaging agents include iodine-125 and technetium-99, with technetium-99 being particularly preferred. Methods for producing protein-isotope conjugates are well known in the art, and are described by, for example, Eckelman *et al.* (U.S. Pat. No. 4,652,440), Parker *et al.* (WO 87/05030) and Wilber *et al.* (EP 203,764). Alternatively, 10 the transferrin fusion proteins may be bound to spin label enhancers and used for magnetic resonance (MR) imaging. Suitable spin label enhancers include stable, sterically hindered, free radical compounds such as nitroxides. Methods for labeling ligands for MR imaging are disclosed by, for example, Coffman *et al.* (U.S. Pat. No. 4,656,026). For 15 administration, the labeled transferrin fusion proteins are combined with a pharmaceutically acceptable carrier or diluent, such as sterile saline or sterile water. Administration is preferably by bolus injection, preferably intravenously.

### **Production of Fusion Proteins**

20 The present invention further provides methods for producing a modified fusion protein of the invention using nucleic acid molecules herein described. In general terms, the production of a recombinant form of a protein typically involves the following steps.

A nucleic acid molecule is first obtained that encodes a transferrin fusion protein of the invention. The nucleic acid molecule is then preferably placed in operable linkage 25 with suitable control sequences, as described above, to form an expression unit containing the protein open reading frame. The expression unit is used to transform a suitable host and the transformed host is cultured under conditions that allow the production of the recombinant protein. Optionally the recombinant protein is isolated from the medium or from the cells; recovery and purification of the protein may not be necessary in some 30 instances where some impurities may be tolerated.

Each of the foregoing steps can be accomplished in a variety of ways. For example, the construction of expression vectors that are operable in a variety of hosts is accomplished using appropriate replicons and control sequences, as set forth above. The

control sequences, expression vectors, and transformation methods are dependent on the type of host cell used to express the gene and were discussed in detail earlier and are otherwise known to persons skilled in the art. Suitable restriction sites can, if not normally available, be added to the ends of the coding sequence so as to provide an excisable gene to insert into these vectors. A skilled artisan can readily adapt any host/expression system known in the art for use with the nucleic acid molecules of the invention to produce a desired recombinant protein.

As discussed above, any expression system may be used, including yeast, bacterial, animal, plant, eukaryotic and prokaryotic systems. In some embodiments, yeast, mammalian cell culture and transgenic animal or plant production systems are preferred. In other embodiments, yeast systems that have been modified to reduce native yeast glycosylation, hyper-glycosylation or proteolytic activity may be used.

### Therapeutic Molecules

Any therapeutic molecule may be used as the fusion partner to Tf according to the methods and compositions of the present invention. As used herein, a therapeutic molecule is typically a protein or peptide capable of exerting a beneficial biological effect *in vitro* or *in vivo* and includes proteins or peptides that exert a beneficial effect in relation to normal homeostasis, physiology or a disease state. Therapeutic molecules do not include, fusion partners commonly used as markers or protein purification aids, such as galactosidases (see for example, U.S. Patent 5, 986, 067 and Aldred *et al.* (1984) *Biochem. Biophys. Res. Commun.* 122: 960-965). For instance, a beneficial effect as related to a disease state includes any effect that is advantageous to the treated subject, including disease prevention, disease stabilization, the lessening or alleviation of disease symptoms or a modulation, alleviation or cure of the underlying defect to produce an effect beneficial to the treated subject.

A modified transferrin fusion protein of the invention includes at least a fragment or variant of a therapeutic protein and at least a fragment or variant of modified serum transferrin, which are associated with one another, preferably by genetic fusion or chemical conjugation.

In one embodiment, the transferrin fusion protein includes a modified transferrin molecule linked to a neuropharmaceutical agent. In another embodiment, the modified transferrin fusion protein includes transferrin at the carboxyl terminus linked to a

neuropharmaceutical agent at the amino terminus. In an alternate embodiment, the modified transferrin fusion protein includes transferrin at the amino terminus linked to a neuropharmaceutical agent at the carboxy terminus. In specific embodiments, the neuropharmaceutical agent is either nerve growth factor or ciliary neurotrophic factor.

5 In further embodiments, a modified transferrin fusion protein of the invention may contain at least a fragment or variant of a therapeutic protein, and/or at least a fragment or variant of an antibody. In a further embodiment, the transferrin fusion proteins can contain peptide fragments or peptide variants of proteins or antibodies wherein the variant or fragment retains at least one biological or therapeutic activity. The transferrin fusion  
10 proteins can contain therapeutic proteins that can be peptide fragments or peptide variants at least about 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 20, at least 25, at least 30, at least 35, or at least about 40, at least about 50, at least about 55, at least about 60 or at least about 70 or more amino acids in length fused to the N and/or C termini, inserted within, or  
15 inserted into a loop of a modified transferrin.

In another embodiment, the modified transferrin fusion molecules contain a therapeutic protein portion that can be fragments of a therapeutic protein that include the full length protein as well as polypeptides having one or more residues deleted from the amino terminus of the amino acid sequence.

20 In another embodiment, the modified transferrin fusion molecules contain a therapeutic protein portion that can be fragments of a therapeutic protein that include the full length protein as well as polypeptides having one or more residues deleted from the carboxy terminus of the amino acid sequence.

In another embodiment, the modified transferrin fusion molecules contain a  
25 therapeutic protein portion that can have one or more amino acids deleted from both the amino and the carboxy termini.

In another embodiment, the modified transferrin fusion molecules contain a therapeutic protein portion that is at least about 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to a reference therapeutic protein set forth herein, or fragments thereof. In  
30 further embodiments, the transferrin fusion molecules contain a therapeutic protein portion that is at least about 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to reference polypeptides having the amino acid sequence of N- and C-terminal deletions as described above.



In another embodiment, the modified transferrin fusion molecules contain the therapeutic protein portion that is at least about 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100%, identical to, for example, the native or wild-type amino acid sequence of a therapeutic protein. Fragments, of these polypeptides are also provided.

5       The therapeutic proteins corresponding to a therapeutic protein portion of a modified transferrin fusion protein of the invention, such as cell surface and secretory proteins, can be modified by the attachment, of one or more oligosaccharide groups. The modification referred to as glycosylation, can significantly affect the physical properties of proteins and can be important in protein stability, secretion, and localization.

10       Glycosylation occurs at specific locations along the polypeptide backbone. There are usually two major types of glycosylation: glycosylation characterized by O-linked oligosaccharides, which are attached to serine or threonine residues; and glycosylation characterized by N-linked oligosaccharides, which are attached to asparagine residues in an Asn-X-Ser/Thr sequence, where X can be an amino acid except proline. Variables such  
15 as protein structure and cell type influence the number and nature of the carbohydrate units within the chains at different glycosylation sites. Glycosylation isomers are also common at the same site within a given cell type. For example, several types of human interferon are glycosylated.

20       Therapeutic proteins corresponding to a therapeutic protein portion of a transferrin fusion protein of the invention, as well as analogs and variants thereof, may be modified so that glycosylation at one or more sites is altered as a result of manipulation(s) of their nucleic acid sequence by the host cell in which they are expressed, or due to other conditions of their expression. For example, glycosylation isomers may be produced by abolishing or introducing glycosylation sites, *e.g.*, by substitution or deletion of amino  
25 acid residues, such as substitution of glutamine for asparagine, or unglycosylated recombinant proteins may be produced by expressing the proteins in host cells that will not glycosylate them, *e.g.* in glycosylation-deficient yeast. These approaches are known in the art.

30       Therapeutic proteins and their nucleic acid sequences are well known in the art and available in public databases such as Chemical Abstracts Services Databases (*e.g.*, the CAS Registry), GenBank, and GenSeq. The Accession Numbers and sequences referred to below are herein incorporated by reference in their entirety.

In other embodiments, the transferrin fusion proteins of the invention are capable of a therapeutic activity and/or biologic activity, corresponding to the therapeutic activity and/or biologic activity of the therapeutic protein listed in the corresponding row of Table 1 and elsewhere in this application. (See, *e.g.*, the “Biological Activity” and “Therapeutic Protein X” columns of Table 1.) In further embodiments, the therapeutically active protein portions of the transferrin fusion proteins of the invention are fragments or variants of the reference sequences cited herein.

The present invention is further directed to modified Tf fusion proteins comprising fragments of the therapeutic proteins herein described. Even if deletion of one or more amino acids from the N-terminus of a protein results in modification or loss of one or more biological functions of the therapeutic protein portion, other therapeutic activities and/or functional activities (*e.g.*, biological activities, ability to multimerize, ability to bind a ligand) may still be retained. For example, the ability of polypeptides with N-terminal deletions to induce and/or bind to antibodies which recognize the complete or mature forms of the polypeptides generally will be retained with less than the majority of the residues of the complete polypeptide removed from the N-terminus. Whether a particular polypeptide lacking N-terminal residues of a complete polypeptide retains such immunologic activities can be assayed by routine methods described herein and otherwise known in the art. It is not unlikely that a mutant with a large number of deleted N-terminal amino acid residues may retain some biological or immunogenic activities. In fact, peptides composed of as few as six amino acid residues may often evoke an immune response.

Also as mentioned above, even if deletion of one or more amino acids from the N-terminus or C-terminus of a therapeutic protein results in modification or loss of one or more biological functions of the protein, other functional activities (*e.g.*, biological activities, ability to multimerize, ability to bind a ligand) and/or therapeutic activities may still be retained. For example the ability of polypeptides with C-terminal deletions to induce and/or bind to antibodies which recognize the complete or mature forms of the polypeptide generally will be retained when less than the majority of the residues of the complete or mature polypeptide are removed from the C-terminus. Whether a particular polypeptide lacking the N-terminal and/or, C-terminal residues of a reference polypeptide retains therapeutic activity can readily be determined by routine methods described herein and/or otherwise known in the art.

Peptide fragments of the therapeutic proteins can be fragments comprising, or alternatively, consisting of, an amino acid sequence that displays a therapeutic activity and/or functional activity (*e.g.* biological activity) of the polypeptide sequence of the therapeutic protein of which the amino acid sequence is a fragment.

5 Other polypeptide fragments are biologically active fragments. Biologically active fragments are those exhibiting activity similar, but not necessarily identical, to an activity of a therapeutic protein used in the present invention. The biological activity of the fragments may include an improved desired activity, or a decreased undesirable activity.

Generally, variants of proteins are overall very similar, and, in many regions,  
10 identical to the amino acid sequence of the therapeutic protein corresponding to a therapeutic protein portion of a transferrin fusion protein of the invention. Nucleic acids encoding these variants are also encompassed by the invention.

Further therapeutic polypeptides that may be used in the invention are polypeptides encoded by polynucleotides which hybridize to the complement of a nucleic acid molecule  
15 encoding an amino acid sequence of a therapeutic protein under stringent hybridization conditions which are known to those of skill in the art. (see, for example, Ausubel, F.M. *et al.*, eds., 1989 Current protocol in Molecular Biology, Green Publishing Associates, Inc., and John Wiley & Sons Inc., New. York). Polynucleotides encoding these polypeptides are also encompassed by the invention.

20 By a polypeptide-having an amino acid sequence at least, for example, 95% "identical" to a query amino acid sequence of the present invention, it is intended that the amino acid sequence of the subject polypeptide is identical to the query sequence except that the subject polypeptide sequence may include up to five amino acid alterations per each 100 amino acids of the query amino acid sequence. In other words, to obtain a  
25 polypeptide having an amino acid sequence at least 95% identical to a query amino acid sequence, up to 5% of the amino acid residues in the subject sequence may be inserted, deleted, or substituted with another amino acid. These alterations of the reference sequence may occur at the amino- or carboxy-terminal positions of the reference amino acid sequence or anywhere between those terminal positions, interspersed either  
30 individually among residues in the reference sequence, or in one or more contiguous groups within the reference sequence.

As a practical matter, whether any particular polypeptide is at least about 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to, for instance, the amino acid

sequence of a transferrin fusion protein of the invention or a fragment thereof (such, as the therapeutic protein portion of the transferrin fusion protein or the transferrin portion of the transferrin fusion protein), can be determined conventionally using known computer programs. A preferred method for determining the best overall match between a query sequence (a sequence of the present invention) and a subject sequence, also referred to as a global sequence alignment, can be determined using the FASTDB computer program based on the algorithm of Brufiga-*et al.* (Comp. App. Biosci 245- (1990)).

The polynucleotide variants of the invention may contain alterations in the coding regions, non-coding regions, or both. Polynucleotide variants containing alterations which produce silent substitutions, additions, or deletions, but do not alter the properties or activities of the encoded polypeptide may be used to produce modified Tf fusion proteins. Nucleotide variants produced by silent substitutions due to the degeneracy of the genetic code can be utilized. Moreover, polypeptide variants in which less than about 50, less than 40, less than 30, less than 20, less than 10, or 5-50, 5-25, 5-10, 1-5, or 1-2 amino acids are substituted, deleted, or added in any combination can also be utilized. Polynucleotide variants can be produced for a variety of reasons, *e.g.*, to optimize codon expression for a particular host (change codons in the human mRNA to those preferred by a host, such as, yeast or *E. coli* as described above).

In other embodiments, the therapeutic protein moiety has conservative substitutions compared to the wild-type sequence. By "conservative substitutions" is intended swaps within groups such as replacement of the aliphatic or hydrophobic amino acids Ala, Val, Leu and Ile; replacement of the hydroxyl residues Ser and Thr; replacement of the acidic residues Asp and Glu; replacement of the amide residues Asn and Gln, replacement of the basic residues Lys, Arg, and His; replacement of the aromatic residues Phe, Tyr, and Trp, and replacement of the small-sized amino acids Ala, Ser, Thr, Met, and Gly. Guidance concerning how to make phenotypically silent amino acid substitutions is provided, for example, in Bowie *et al.*, "Deciphering the Message in Protein Sequences: Tolerance to Amino Acid Substitutions," Science 247:1306-1310 (1990). In specific embodiments, the polypeptides of the invention comprise, or alternatively, consist of, fragments or variants of the amino acid sequence of a therapeutic protein described herein and/or serum transferrin, and/ modified transferrin protein of the invention, wherein the fragments or variants have 1-5, 5-10, 5-25, 5-50, 10-50 or 50-150 amino acid residue additions, substitutions, and/or deletions when compared to the

reference amino acid sequence. In further embodiments, the amino acid substitutions are conservative. Nucleic acids encoding these polypeptides are also encompassed by the invention.

5 The modified fusion proteins of the present invention can be composed of amino-acids joined to each other by peptide bonds or modified peptide bonds and may contain amino acids other than the 20 gene-encoded amino acids. The polypeptides may be modified by either natural processes, such as post-translational processing, or by chemical modification techniques which are well known in the art. Such modifications are well described in basic texts and in more detailed monographs, as well as in a voluminous  
10 research literature.

Modifications can occur anywhere in a polypeptide, including the peptide backbone, the amino acid side-chains and the amino or carboxy termini. It will be appreciated that the same type of modification may be present in the same or varying degrees at several sites in a given polypeptide. Also, a given polypeptide may contain  
15 many types of modifications. Polypeptides may be branched, for example, as a result of ubiquitination, and they may be cyclic, with or without branching. Cyclic, branched, and branched cyclic polypeptides may result from posttranslation natural processes or may be made by synthetic methods. Modifications include acetylation, acylation, ADP-ribosylation, amidation, covalent attachment of flavin, covalent attachment of a heme  
20 moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphatidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent cross-links, formation of cysteine, glycosylation, GPI anchor formation, hydroxylation, iodination, methylation, myristylation, oxidation, pegylation, proteolytic processing, phosphorylation,  
25 prenylation, racemization, sulfation, transfer-RNA mediated addition of amino acids to proteins such as arginylation, and ubiquitination. (See, for instance, PROTEINS – STRUCTURE AND MOLECULAR PROPERTIES, 2nd Ed., T. E. Creighton, W. H. Freeman and Company, New York(1993); POST-TRANSLATIONAL COVALENT MODIFICATION OF PROTEINS, B. C. Johnson, Ed., Academic Press, New' York, pgs. 1-12 (1983); Seifter  
30 *et al.* (1990) *Meth. Enzymol.* 182:626-646; Rattan *et al.*, *Ann. N.Y. Acad. Sci.* 663:48-62.

Therapeutic molecules that may be fused to or inserted into Tf include, but are not limited to, hormones, matrix proteins, immunosuppressants, bronchodilators, cardiovascular agents, enzymes, CNS agents, neurotransmitters, receptor proteins or

peptides, growth hormones, growth factors, antiviral peptides, fusogenic inhibitor peptides, cytokines, lymphokines, monokines, interleukins, colony stimulating factors, differentiation factors, angiogenic factors, receptor ligands, cancer-associated proteins, antineoplastics, viral peptides, antibiotic peptides, blood proteins, antagonist proteins, transcription factors, anti-angiogenic factors, antagonist proteins or peptides, receptor antagonists, antibodies, single chain antibodies and cell adhesion molecules. Different therapeutic molecules may be combined into a single fusion protein to produce a bi or multi-functional therapeutic molecule. Different molecules may also be used in combination to produce a fusion protein with a therapeutic entity and a targeting entity.

Cytokines are soluble proteins released by cells of the immune system, which act nonenzymatically through specific receptors to regulate immune responses. Cytokines resemble hormones in that they act at low concentrations bound with high affinity to a specific receptor. The term "cytokine" is used herein to describe naturally occurring or recombinant proteins, analogs thereof, and fragments thereof which elicit a specific biological response in a cell which has a receptor for that cytokine. Cytokines preferably include interleukins such as interleukin-2 (IL-2) (GenBank Acc. No. S77834), IL-3 (GenBank Acc. No. M14743), IL-4 (GenBank Acc. No. M23442), IL-5 (GenBank Acc. No. J03478), IL-6 (GenBank Acc. No. M14584), IL-7 (GenBank Acc. No. NM\_000880), IL-10 (GenBank Acc. No. NM\_000572), IL-12 (GenBank Acc. No. AF180562 and GenBank Acc. No. AF180563), IL-13 (GenBank Acc. No. U10307), IL-14 (GenBank Acc. No. XM\_170924), IL-15 (GenBank Acc. No. X91233), IL-16 (GenBank Acc. No. NM\_004513), IL-17 (GenBank Acc. No. NM\_002190) and IL-18 (GenBank Acc. No. NM\_001562), hematopoietic factors such as granulocyte-macrophage colony stimulating factor (GM-CSF) (GenBank Acc. No. X03021), granulocyte colony stimulating factor (G-CSF) (GenBank Acc. No. X03656), platelet activating factor (GenBank Acc. No. NM\_000437) and erythropoietin (GenBank Acc. No. X02158), tumor necrosis factors (TNF) such as TNF $\alpha$  (GenBank Acc. No. X02910), lymphokines such as lymphotoxin- $\alpha$  (GenBank Acc. No. X02911), lymphotoxin- $\beta$  (GenBank Acc. No. L11016), leukoregulin, macrophage migration inhibitory factor (GenBank Acc. No. M25639), and neuroleukin (GenBank Acc. No. K03515), regulators of metabolic processes such as leptin (GenBank Acc. No. U43415), interferons such as interferon  $\alpha$  (IFN $\alpha$ ) (GenBank Acc. No. M54886), IFN $\beta$  (GenBank Acc. No. V00534), IFN $\gamma$  (GenBank Acc. No. J00219), IFN $\delta$  (GenBank Acc. No. NM\_002177), thrombospondin 1 (THBS1) (GenBank Acc. No. NM\_003246),

THBS2 (GenBank Acc. No. L12350), THBS3 (GenBank Acc. No. L38969), THBS4 (GenBank Acc. No. NM\_003248), and chemokines. Preferably, the modified transferrin-cytokine fusion protein of the present invention displays cytokine biological activity.

The term "hormone" is used herein to describe any one of a number of biologically active substances that are produced by certain cells or tissues and that cause specific biological changes or activities to occur in another cell or tissue located elsewhere in the body. Hormones preferably include proinsulin (GenBank Acc. No. V00565), insulin (GenBank Acc. No. NM\_000207), growth hormone 1 (GenBank Acc. No. V00520), growth hormone 2 (GenBank Acc. No. F006060), growth hormone release factor (GenBank Acc. No. NM\_021081), insulin-like growth factor I (GenBank Acc. No. M27544), insulin-like growth factor II (GenBank Acc. No. NM\_000612), insulin-like growth factor binding protein 1 (IGFBP-1) (GenBank Acc. No. M59316), IGFBP-2 (GenBank Acc. No. X16302), IGFBP-3 (GenBank Acc. No. NM\_000598), IGFBP-4 (GenBank Acc. No. Y12508), IGFBP-5 (GenBank Acc. No. M65062), IGFBP-6 (GenBank Acc. No. NM\_002178), IGFBP-7 (GenBank Acc. No. NM\_001553), chorionic gonadotropin  $\beta$  chain (GenBank Acc. No. NM\_033142), chorionic gonadotropin  $\alpha$  chain (GenBank Acc. No. NM\_000735), luteinizing hormone  $\beta$  (GenBank Acc. No. X00264), follicle-stimulating hormone  $\beta$  (GenBank Acc. No. NM\_000510), thyroid-stimulating hormone  $\beta$  (GenBank Acc. No. NM\_000549), prolactin (GenBank Acc. No. NM\_000948), pro-opiomelanocortin (GenBank Acc. No. V01510), corticotropin (ACTH),  $\beta$ -lipotropin,  $\alpha$ -melanocyte stimulating hormone ( $\alpha$ -MSH),  $\gamma$ -lipotropin,  $\beta$ -MSH,  $\beta$ -endorphin, and corticotropin-like intermediate lobe peptide (CLIP).

The term "growth factor" is used herein to describe any protein or peptide that binds to a receptor to stimulate cell proliferation. Growth factors preferably include platelet-derived growth factor- $\alpha$  (PDGF- $\alpha$ ) (GenBank Acc. No. X03795), PDGF- $\beta$  (GenBank Acc. No. X02811), steroid hormones, epidermal growth factor (EGF) (GenBank Acc. No. NM\_001963), fibroblast growth factors such as fibroblast growth factor 1 (FGF1) (GenBank Acc. No. NM\_000800), FGF2 (GenBank Acc. No. NM\_002006), FGF3 (GenBank Acc. No. NM\_005247), FGF4 (GenBank Acc. No. NM\_002007), FGF5 (GenBank Acc. No. M37825), FGF6 (GenBank Acc. No. X57075), FGF7 (GenBank Acc. No. NM\_002009), FGF8 (GenBank Acc. No. AH006649), FGF9 (GenBank Acc. No. NM\_002010), FGF10 (GenBank Acc. No. AB002097), FGF11 (GenBank Acc. No. NM\_004112), FGF12 (GenBank Acc. No. NM\_021032), FGF13

(GenBank Acc. No. NM\_004114), FGF14 (GenBank Acc. No. NM\_004115), FGF16 (GenBank Acc. No. AB009391), FGF17 (GenBank Acc. No. NM\_003867), FGF18 (GenBank Acc. No. AF075292), FGF19 (GenBank Acc. No. NM\_005117), FGF20 (GenBank Acc. No. NM\_019851), FGF21 (GenBank Acc. No. NM\_019113), FGF22 (GenBank Acc. No. NM\_020637), and FGF23 (GenBank Acc. No. NM\_020638), angiogenin (GenBank Acc. No. M11567), brain-derived neurotrophic factor (GenBank Acc. No. M61176), ciliary neurotrophic growth factor (GenBank Acc. No. X60542), transforming growth factor- $\alpha$  (TGF- $\alpha$ ) (GenBank Acc. No. X70340), TGF- $\beta$  (GenBank Acc. No. X02812), nerve growth factor- $\alpha$  (NGF- $\alpha$ ) (GenBank Acc. No. NM\_010915), NGF- $\beta$  (GenBank Acc. No. X52599), tissue inhibitor of metalloproteinase 1 (TIMP1) (GenBank Acc. No. NM\_003254), TIMP2 (GenBank Acc. No. NM\_003255), TIMP3 (GenBank Acc. No. U02571), TIMP4 (GenBank Acc. No. U76456) and macrophage stimulating 1 (GenBank Acc. No. L11924).

The term "matrix protein" is used herein to describe proteins or peptides that are normally found in the extracellular matrix. These proteins may be functionally important for strength, filtration, or adhesion. Matrix proteins preferably include collagens such as collagen I (GenBank Acc. No. Z74615), collagen II (GenBank Acc. No. X16711), collagen III (GenBank Acc. No. X14420), collagen IV (GenBank Acc. No. NM\_001845), collagen V (GenBank Acc. No. NM\_000393), collagen VI (GenBank Acc. No. NM\_058175), collagen VII (GenBank Acc. No. L02870), collagen VIII (GenBank Acc. No. NM\_001850), collagen IX (GenBank Acc. No. X54412), collagen X (GenBank Acc. No. X60382), collagen XI (GenBank Acc. No. J04177), and collagen XII (GenBank Acc. No. U73778), laminin proteins such as LAMA2 (GenBank Acc. No. NM\_000426), LAMA3 (GenBank Acc. No. L34155), LAMA4 (GenBank Acc. No. NM\_002290), LAMB1 (GenBank Acc. No. NM\_002291), LAMB3 (GenBank Acc. No. L25541), LAMC1 (GenBank Acc. No. NM\_002293), nidogen (GenBank Acc. No. NM\_002508),  $\alpha$ -tectorin (GenBank Acc. No. NM\_005422),  $\beta$ -tectorin (GenBank Acc. No. NM\_058222), and fibronectin (GenBank Acc. No. X02761).

The term "blood proteins" are traditionally defined as those sourced from plasma, many now commonly produced by recombinant means, and include, but are not limited to native serum proteins, derivatives, fragments and mutants or variants thereof, blood clotting factors, derivatives, mutants, variants and fragments (including factors VII, VIII, IX, X), protease inhibitors (antithrombin 3, alpha-1 antitrypsin), urokinase-type



plasminogen activator, immunoglobulins, von Willebrand factor and von Willebrand mutants, fibronectin, fibrinogen, thrombin and hemoglobin.

The term “enzyme” is used herein to describe any protein or proteinaceous substance which catalyzes a specific reaction without itself being permanently altered or destroyed. Enzymes preferably include coagulation factors such as F2 (GenBank Acc. No. XM\_170688), F7 (GenBank Acc. No. XM\_027508), F8 (GenBank Acc. No. XM\_013124), F9 (GenBank Acc. No. NM\_000133), F10 (GenBank Acc. No. AF503510) and others, matrix metalloproteinases such as matrix metalloproteinase I (GenBank Acc. No. MMP1) (GenBank Acc. No. NM\_002421), MMP2 (GenBank Acc. No. NM\_004530), MMP3 (GenBank Acc. No. NM\_002422), MMP7 (GenBank Acc. No. NM\_002423), MMP8 (GenBank Acc. No. NM\_002424), MMP9 (GenBank Acc. No. NM\_004994), MMP10 (GenBank Acc. No. NM\_002425), MMP12 (GenBank Acc. No. NM\_002426), MMP13 (GenBank Acc. No. X75308), MMP20 (GenBank Acc. No. NM\_004771), adenosine deaminase (GenBank Acc. No. NM\_000022), mitogen activated protein kinases such as MAPK3 (GenBank Acc. No. XM\_055766), MAP2K2 (GenBank Acc. No. NM\_030662), MAP2K1 (GenBank Acc. No. NM\_002755), MAP2K4 (GenBank Acc. No. NM\_003010), MAP2K7 (AF013588), and MAPK12 (NM\_002969), kinases such as JNKK1 (GenBank Acc. No. U17743), JNKK2 (GenBank Acc. No. AF014401), JAK1 (M64174), JAK2 (NM\_004972), and JAK3 (NM\_000215), and phosphatases such as PPM1A (GenBank Acc. No. NM\_021003) and PPM1D (GenBank Acc. No. NM\_003620).

The term “transcription factors” is used herein to describe any protein or peptide involved in the transcription of protein-coding genes. Transcription factors may include Sp1, Sp2 (GenBank Acc. No. NM\_003110), Sp3 (GenBank Acc. No. AY070137), Sp4 (GenBank Acc. No. NM\_003112) NFYB (GenBank Acc. No. NM\_006166), Hap2 (GenBank Acc. No. M59079), GATA-1 (GenBank Acc. No. NM\_002049), GATA-2 (GenBank Acc. No. NM\_002050), GATA-3 (GenBank Acc. No. X55122), GATA-4 (GenBank Acc. No. L34357), GATA-5, GATA-6 (GenBank Acc. No. NM\_005257), FOG2 (NM\_012082), Eryf1 (GenBank Acc. No. X17254), TRPS1 (GenBank Acc. No. NM\_014112), NF-E2 (GenBank Acc. No. NM\_006163), NF-E3, NF-E4, TFCEP2 (GenBank Acc. No. NM\_005653), Oct-1 (GenBank Acc. No. X13403), homeobox proteins such as HOXB2 (GenBank Acc. No. NM\_002145), HOX2H (GenBank Acc. No. X16665), hairless homolog (GenBank Acc. No. NM\_005144), mothers against decapentaplegic proteins such as MADH1 (GenBank Acc. No. NM\_005900), MADH2

(GenBank Acc. No. NM\_005901), MADH3 (GenBank Acc. No. NM\_005902), MADH4 (GenBank Acc. No. NM\_005359), MADH5 (GenBank Acc. No. AF009678), MADH6 (GenBank Acc. No. NM\_005585), MADH7 (GenBank Acc. No. NM\_005904), MADH9 (GenBank Acc. No. NM\_005905), and signal transducer and activator of transcription proteins such as STAT1 (GenBank Acc. No. XM\_010893), STAT2 (GenBank Acc. No. NM\_005419), STAT3 (GenBank Acc. No. AJ012463), STAT4 (GenBank Acc. No. NM\_003151), STAT5 (GenBank Acc. No. L41142), and STAT6 (GenBank Acc. No. NM\_003153).

In yet another embodiment of the invention, the therapeutic molecule is a non-human or non-mammalian protein. For example, HIV gp120, HIV Tat, surface proteins of other viruses such as hepatitis, herpes, influenza, adenovirus and RSV, other HIV components, parasitic surface proteins such as malarial antigens, and bacterial surface proteins are preferred. These non-human proteins may be used, for example, as antigens, or because they have useful activities. For example, the therapeutic molecule may be streptokinase, staphylokinase, urokinase, or other proteins with useful enzymatic activities.

In an alternative embodiment, the therapeutic molecule is a ligand-binding protein with biological activity. Such ligand-binding proteins may, for example, (1) block receptor-ligand interactions at the cell surface; or (2) neutralize the biological activity of a molecule in the fluid phase of the blood, thereby preventing it from reaching its cellular target. In some embodiments, the modified transferrin fusion proteins include a modified transferrin molecule fused to a ligand-binding domain of a receptor selected from the group consisting of, but not limited to, a low density lipoprotein (LDL) receptor, an acetylated LDL receptor, a tumor necrosis factor  $\alpha$  receptor, a transforming growth factor  $\beta$  receptor, a cytokine receptor, an immunoglobulin Fc receptor, a hormone receptor, a glucose receptor, a glycolipid receptor, and a glycosaminoglycan receptor. In other embodiments, ligand-binding proteins include CD2 (M14362), CD3G (NM\_000073), CD3D (NM\_000732), CD3E (NM\_000733), CD3Z (J04132), CD28 (NM\_006139), CD4 (GenBank Acc. No. NM\_000616), CD1A (GenBank Acc. No. M28825), CD1B (GenBank Acc. No. NM\_001764), CD1C (GenBank Acc. No. NM\_001765), CD1D (GenBank Acc. No. NM\_001766), CD80 (GenBank Acc. No. NM\_005191), GNB3 (GenBank Acc. No. AF501884), CTLA-4 (GenBank Acc. No. NM\_005214), intercellular adhesion molecules such as ICAM-1 (NM\_000201), ICAM-2 (NM\_000873), and ICAM-3 (NM\_002162), tumor necrosis factor receptors such as TNFRSF1A (GenBank Acc. No. X55313),

TNFR1SFB (GenBank Acc. No. NM\_001066), TNFRSF9 (GenBank Acc. No. NM\_001561), TNFRSF10B (GenBank Acc. No. NM\_003842), TNFRSF11B (GenBank Acc. No. NM\_002546), and TNFRSF13B (GenBank Acc. No. NM\_006573), and interleukin receptors such as IL2RA (GenBank Acc. No. NM\_000417), IL2RG (GenBank  
 5 Acc. No. NM\_000206), IL4R (GenBank Acc. No. AF421855), IL7R (GenBank Acc. No. NM\_002185), IL9R (GenBank Acc. No. XM\_015989), and IL13R (GenBank Acc. No. X95302). Preferably, the Tf-ligand-binding protein fusion of the present invention displays the biological activity of the ligand-binding protein.

The term “cancer-associated proteins” is used herein to describe proteins or  
 10 polypeptides whose expression is associated with cancer or the maintenance of controlled cell growth, such as proteins encoded by tumor suppressor genes or oncogenes. Cancer-associated proteins may be p16 (GenBank Acc. No. AH005371), p53 (GenBank Acc. No. NM\_000546), p63 (GenBank Acc. No. NM\_003722), p73 (GenBank Acc. No. NM\_005427), BRCA1 (GenBank Acc. No. U14680), BRCA2 (GenBank Acc. No.  
 15 NM\_000059), CTBP interacting protein (GenBank Acc. No. U72066), DMBT1 (GenBank Acc. No. NM\_004406), HRAS (GenBank Acc. No. NM\_005343), NCYM (GenBank Acc. No. NM\_006316), FGR (GenBank Acc. No. NM\_005248), myb (GenBank Acc. No. AF104863), raf1 (GenBank Acc. No. NM\_002880), erbB2 (GenBank Acc. No. NM\_004448), VAV (GenBank Acc. No. X16316), c-fos (V GenBank Acc. No. 01512), c-  
 20 fes (GenBank Acc. No. X52192), c-jun (GenBank Acc. No. NM\_002228), MAS1 (GenBank Acc. No. M13150), pim-1 (GenBank Acc. No. M16750), TIF1 (GenBank Acc. No. NM\_003852), c-fms (GenBank Acc. No. X03663), EGFR (GenBank Acc. No. NM\_005228), erbA (GenBank Acc. No. X04707), c-src tyrosine kinase (GenBank Acc. No. XM\_044659), c-abl (GenBank Acc. No. M14752), N-ras (GenBank Acc. No.  
 25 X02751), K-ras (GenBank Acc. No. M54968), jun-B (GenBank Acc. No. M29039), c-myc (GenBank Acc. No. AH001511), RB1 (GenBank Acc. No. M28419), DCC (GenBank Acc. No. X76132), APC (GenBank Acc. No. NM\_000038), NF1 (GenBank Acc. No. M89914), NF2 (GenBank Acc. No. Y18000), and bcl-2 (GenBank Acc. No. M13994).

“Fusogenic inhibitor peptides” is used herein to describe peptides that show  
 30 antiviral activity, anti-membrane fusion capability, and/or an ability to modulate intracellular processes, for instance, those involving coiled-coil peptide structures. Antiviral activity includes, but is not limited to, the inhibition of HIV-1, HIV-2, RSV, SIV, EBV, Measles virus, influenza virus, or CMV transmission to uninfected cells.

Additionally, the antifusogenic capability, antiviral activity or intracellular modulatory activity of the peptides merely requires the presence of the peptides and specifically does not require the stimulation of a host immune response directed against such peptides.

Antifusogenic refers to a peptide's ability to inhibit or reduce the level of membrane

5 fusion events between two or more moieties relative to the level of membrane fusion which occurs between said moieties in the absence of the peptide. The moieties may be, for example, cell membranes or viral structures, such as viral envelopes or pili. The term "antiviral peptide", as used herein, refers to the peptide's ability to inhibit viral infection of cells or some viral activity required for productive viral infection and/or viral  
10 pathogenesis, via, for example, cell-cell fusion or free virus infection. Such infection may involve membrane fusion, as occurs in the case of enveloped viruses, or some other fusion event involving a viral structure and a cellular structure. Fusogenic inhibitor peptides and antiviral peptides often have amino acid sequences that are derived from greater than one viral protein (*e.g.*, an HIV-1, HIV-2, RSV, and SIV-derived polypeptide).

15 Examples of fusogenic inhibitor peptides and antiviral peptides can be found in WO 94/2820, WO 96/19495, WO 96/40191, WO 01/64013 and US patents 6,333,395, 6,258,782, 6,228,983, 6,133,418, 6,093,794, 6,068,973, 6,060,065, 6,054,265, 6,020,459, 6,017,536, 6,013,263, 5,464,933, 5,346,989, 5,603,933, 5,656,480, 5,759,517, 6,245,737; 6,326,004, and 6,348,568; all of which are herein incorporated by reference. In a  
20 preferred embodiment, antifusogenic peptides are selected from the group consisting of HIV T-20 (FWNWLSAWKDLELLEQENKEQQNQSEEILSHILSTY, SEQ ID NO: 4), HIV T-1249, RSV T786 (VYPSDEYDASISQVNEEINQALAYIRKADELLENV, SEQ ID NO: 5), RSV T1584 (AVSKVLHLEGEVNIKISALLSTNKAVVSLSNGVSVLTSKVLDLKNYIDKQL, SEQ  
25 ID NO: 6) and RSV T112 (VFPSDEFDASISQVNEKINQSLAFIRESDELLHNV, SEQ ID NO: 7).

Examples of other types of peptides, include fragments of therapeutic proteins as described herein, in particular, fragments of human proteins that retain at least one activity of the parent molecule. Peptides that may be used to produce modified TF fusion proteins  
30 of the invention also include mimetic peptides and peptides that exhibit a biological activity of a therapeutic protein but differ in sequence or three-dimensional structure from a full-length therapeutic protein. As a non-limited example, peptides include erythropoietin mimetic peptides disclosed by Johnson *et al.* (2000) *Nephrol. Dial.*

*Transplant* 15(9): 1274-7, Kuai *et al.* (2000) *J. Pept. Res.* 56(2):59-62, Barbone *et al.* (1999) *Nephrol. Dial. Transplant.* 14 Supp 2:80-4, Middleton *et al.* (1999) *J. Biol. Chem.* 274(20):14163-9, Johnson *et al.* (1998) *Biochemistry* 37(11):3699-710, Johnson *et al.* (1997) *Chem. Biol.* 12:939-50, Wrighton *et al.* (1997) *Nat. Biotechnol.* 15(12):1261-5, Livnah *et al.* (1996) *Science* 273:464-71, and Wrighton *et al.*, (1996) *Science* 273:458-64.

Therapeutic molecules also include allergenic proteins and digested fragments thereof. These include pollen allergens from ragweed, rye, June grass, orchard grass, sweet vernal grass, red top grass, timothy grass, yellow dock, wheat, corn, sagebrush, blue grass, California annual grass, pigweed, Bermuda grass, Russian thistle, mountain cedar, oak, box elder, sycamore, maple, elm, etc., dust and mites, bee venom, food allergens, animal dander, and other insect venoms.

Other therapeutic molecules include microbial vaccines which include viral, bacterial and protozoal vaccines and their various components such as surface antigens. These include vaccines which contain glycoproteins, proteins or peptides derived from these proteins. Such vaccines are prepared from *Staphylococcus aureus*, *Streptococcus pyogenes*, *Streptococcus pneumonia*, *Neisseria meningitidis*, *Neisseria gonorrhoeae*, *Salmonellae species*, *Shigellae species*, *Escherichia coli*, *Klebsiellae species*, *Proteus species*, *Vibrio cholera*, *Campylobacter pylori*, *Pseudomonas aeruginosa*, *Haemophilus influenzae*, *Bordetella pertussis*, *Mycobacterium tuberculosis*, *Legionella pneumophila*, *Treponema pallidum*, chlamydia, tetanus toxoid, diphtheria toxoid, influenza viruses, adenoviruses, paramyxoviruses (mumps, measles), rubella viruses, polio viruses, hepatitis viruses, herpes viruses, rabies virus, HIV-1, HIV-2, RSV and papilloma viruses.

Preferred fusion molecules may contain anti-HIV viral peptides, anti-RSV peptides, human growth hormone,  $\alpha$  and/or  $\beta$  interferons, erythropoietin (EPO), EPO like peptides, granulocyte-colony stimulating factor (GCSF), granulocyte-macrophage colony-stimulating factor (GMCSF), insulin, insulin-like growth factor (IGF), thrombopoietin, peptides corresponding to the CDR of an antibody, Islet Neogenesis Associated Protein (INGAP), calcitonin, angiostatin, endostatin, interleukin-2, growth hormone releasing factor, human parathyroid hormone, anti-tumor necrosis factor (TNF) peptides, interleukin-1 (IL-1) receptor and/or single chain antibodies.

Fusion proteins of the invention may also be prepared to include peptides or polypeptides derived from peptide libraries to screen for molecules with new or novel functions. Such peptide libraries may include those commercially or publicly available,

*e.g.*, American Peptide Co. Inc., Cell Sciences Inc., Invitrogen Corporation, Phoenix Pharmaceuticals Inc., United States Biological, as well as those produced by available technologies, *e.g.*, bacteriophage and bacterial display libraries made using standard procedures.

5 In yet other embodiments of the invention, Tf fusion proteins may be prepared by using therapeutic protein moieties as known in the art and exemplified by the peptides and proteins currently approved by the Food and Drug Administration at ([www.fda.gov/cber/eoi/approve.htm](http://www.fda.gov/cber/eoi/approve.htm)) as well as PCT Patent Publication Nos. WO 01/79258, WO 01/77137, WO 01/79442, WO 01/79443, WO 01/79444 and WO 10 01/79480, all of which are herein incorporated by reference in their entirety.

Table 1 (adapted from PCT International Publication No. WO 01/79444) provides a non-exhaustive list of therapeutic proteins that correspond to a therapeutic protein portion of a modified transferrin fusion protein of the invention. The "Therapeutic Protein X" column discloses therapeutic protein molecules followed by parentheses containing 15 scientific and brand names that comprise or alternatively consist of that therapeutic protein molecule or a fragment or variant thereof. "Therapeutic protein X" as used herein may refer either to an individual therapeutic protein molecule (as defined by the amino acid sequence obtainable from the CAS and Genbank accession numbers), or to the entire group of therapeutic proteins associated with a given therapeutic protein molecule 20 disclosed in this column. The 'Exemplary Identifier' column provides Chemical Abstracts Services (CAS) Registry Numbers (published by the American Chemical Society) and/or Genbank Accession Numbers (*e.g.*, Locus ID, NP - XXXXX (Reference Sequence Protein), and XP-XXXXX (Model Protein) identifiers available through the national, Center for Biotechnology Information (NCBI) webpage at [www.ncbi.nlm.nih.gov](http://www.ncbi.nlm.nih.gov)) that 25 correspond to entries in the CAS Registry or Genbank database which contain an amino acid sequence of the protein molecule or of a fragment or variant of the therapeutic protein molecule. In addition GenSeq Accession numbers and/or journal publication citations are given to identify the exemplary amino acid sequence for some polypeptides.

The summary pages associated with each of these CAS and Genbank and GenSeq 30 Accession Numbers as well as the cited journal publications are available (*e.g.*, PubMed ID number (PMID)) and are herein incorporated by reference in their entirety. The PCT/Patent Reference column provides U. S. Patent numbers, or PCT International Publication Numbers corresponding to patents and/or published patent- applications that

describe the therapeutic protein molecule all of which are herein incorporated by reference in their entirety. The Biological Activity column describes biological activities associated with the therapeutic protein molecule. The Exemplary Activity Assay column provides references that describe assays which may be used to test the therapeutic and/or biological activity of a therapeutic protein or a transferrin fusion protein of the invention comprising a therapeutic protein X portion. These references are also herein incorporated by reference in their entirety. "The Preferred Indication Y" column describes disease, disorders, and/or conditions that may be treated, prevented, diagnosed, or ameliorated by therapeutic protein X or a transferrin fusion protein of the invention comprising a therapeutic protein X portion.

TABLE 1

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
BMP-1	GeneSeq Accession P80618	WO8800205	BMP1 belongs to the transforming growth factor-beta (TGFB) superfamily. Bone morphogenic proteins induce cartilage and bone formation, play an important role in nephrogenesis, and play an important role in the development of many organs, including lung, heart, teeth, gut, skin, and particularly the kidney.	BMP-1 activity can be determined using the following assays known in the art: Nat Genet. 2001 Jan;27(1):84-8; Eur J Biochem 1996 Apr 1;237(1):295-302; J Biol Chem, Vol. 274, Issue 16, 10897-10902, April 16, 1999; and Hogan, B. L. M. (1996) Genes Dev. 10, 1580-1594.	Induction of Cartilage, Tissue and Bone Growth, and Diabetes
BMP-2	GeneSeq Accession P80619	WO8800205	BMP-2 belongs to the transforming growth factor-beta (TGFB) superfamily. Bone morphogenic protein induces bone formation.	BMP-2 activity can be determined using the following assays known in the art: Nat Genet. 2001 Jan; 27(1):84-8; Eur J Biochem 1996 Apr 1;237(1):295-302; J Biol Chem, Vol. 274, Issue 16, 10897-10902, April 16, 1999; and Hogan, B. L. M. (1996) Genes Dev. 10, 1580-1594.	Induction of Cartilage, Tissue and Bone Growth, and Diabetes
BMP-2B	GeneSeq Accession W24850	US5631142	BMP-2b belongs to the transforming growth factor-beta (TGFB) superfamily. Bone morphogenic protein induces bone formation.	BMP-2b activity can be determined using the following assays known in the art: Nat Genet. 2001 Jan; 27(1):84-8; Eur J Biochem 1996 Apr 1;237(1):295-302; J Biol Cbore, Vol. 274, Issue 16, 10897-10902, April 16, 1999; and Hogan, B. L. M. (1996) Genes Dev. 10, 1580-1594.	Induction of Cartilage, Tissue and Bone Growth, and Diabetes
BMP-4	GeneSeq Accession B02796	WO0020591	BMP-4 belongs to the transforming growth factor-beta (TGFB) superfamily. Bone morphogenic protein induces bone formation.	BMP-4 activity can be determined using the following assays known in the art: Nat Genet. 2001 Jan; 27(1):84-8; Eur J Biochem 1996 Apr 1; 237(1):295-302; J Biol Chem, Vol. 274, Issue 16, 10897-10902, April 16, 1999; and Hogan, B. L. M. (1996) Genes Dev. 10, 1580-1594.	Induction of Cartilage, Tissue and Bone Growth, and Diabetes



Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
BMP-5	GeneSeq Accession B02797	WO0020591	BMP-5 belongs to the transforming growth factor-beta (TGFB) superfamily. Bone morphogenic protein induces bone formation.	BMP-5 activity can be determined using the following assays known in the art: Nat Genet. 2001 Jan; 27(1):84-8; Eur J Biochem 1996 Apr 1; 237(1):295-302; J Biol Chem, Vol. 274, Issue 16, 10897-10902, April 16, 1999; and Hogan, B. L. M. (1996) Genes Dev. 10, 1580-1594.	Induction of Cartilage, Tissue and Bone Growth, and Diabetes
BMP-6	GeneSeq Accession R32904	US5187076	BMP-6 belongs to the transforming growth factor-beta (TGFB) superfamily. Bone morphogenic protein induces bone formation.	BMP-6 activity can be determined using the following assays known in the art: Nat Genet. 2001 Jan; 27(1):84-8; Eur J Biochem 1996 Apr 1; 237(1):295-302; J Biol Chem, Vol. 274, Issue 16, 10897-10902, April 16, 1999; and Hogan, B. L. M. (1996) Genes Dev. 10, 1580-1594.	Induction of Cartilage, Tissue and Bone Growth, and Diabetes
Osteogenic Protein-1; OP-1; BMP-7	GeneSeq Accession W34783	WO973462	OP-1 belongs to the transforming growth factor-beta (TGFB) superfamily. Bone morphogenic protein induces bone formation.	OP-1 activity can be determined using the following assays known in the art: Nat Genet. 2001 Jan; 27(1):84-8; Eur J Biochem 1996 Apr 1; 237(1):295-302; J Biol Chem, Vol. 274, Issue 16, 10897-10902, April 16, 1999; and Hogan, B. L. M. (1996) Genes Dev. 10, 1580-1594.	Induction of Cartilage, Tissue and Bone Growth, and Diabetes
Osteogenic Protein-2	GeneSeq Accession R57973	WO9406399	OP-2 belongs to the transforming growth factor-beta (TGFB) superfamily. Bone morphogenic protein induces bone formation.	OP-2 activity can be determined using the following assays known in the art: Nat Genet. 2001 Jan; 27(1):84-8; Eur J Biochem 1996 Apr 1; 237(1):295-302; J Biol Chem, Vol. 274, Issue 16, 10897-10902, April 16, 1999; and Hogan, B. L. M. (1996) Genes Dev. 10, 1580-1594.	Induction of Cartilage, Tissue and Bone Growth, and Diabetes

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
GDP-1	GeneSeq Accession R60961	WO9406449	Members of the TGF-beta family of proteins initiate cell signaling by binding to heteromeric receptor complexes of type I (TbetaRI) and type II (TbetaRII) serine/threonine kinase receptors (reviewed by Massague, J. et al. (1994) Trends Cell Biol. 4:172-178; Miyazono, K. et al. (1994) Adv. Immunol. 55:181-220). Activation of this heteromeric receptor complex occurs when TGF-beta binds to TbetaRII, which then recruits and phosphorylates TbetaRI. Activated TbetaRI then propagates the signal to downstream targets (Chen, F. and Weinberg, R. A. (1995) PNA892:1565-1569; Wrana, J.L. et al. (1994) Nature 370:341-347).	The effect of GDF-1 on signaling can be assayed by treating Primary BAECs transfected with a construct called p3TP-Lux, containing a TGF-beta responsive promoter fused to a reporter gene, and measuring luciferase gene expression (Wrana et al., 1994, Nature 370: 341-347).	Developmental disorders, Induction of Cartilage, Tissue and Bone Growth, and Diabetes
BMP-9	GeneSeq Accession R86903	WO9533830	BMP-9 belongs to the transforming growth factor-beta (TGFB) superfamily. Bone morphogenic protein induces bone formation.	BMP-9 activity can be determined using the following assays known in the art: Nat Genet. 2001 Jan; 27(1):84-8; Eur J Biochem 1996 Apr 1; 237(1):295-302; J Biol Chem, Vol. 274, Issue 16, 10897-10902, April 16, 1999; and Hogan, B. L. M. (1996) Genes Dev. 10, 1580-1594.	Induction of Cartilage, Tissue and Bone Growth, and Diabetes
BMP-10	GeneSeq Accession R66202	WO9426893	BMP-10 belongs to the transforming growth factor-beta (TGFB) superfamily. Bone morphogenic protein induces bone formation.	BMP-10 activity can be determined using the following assays known in the art: Nat Genet. 2001 Jan; 27(1):84-8; Eur J Biochem 1996 Apr 1; 237(1):295-302; J Biol Chem, Vol. 274, Issue 16, 10897-10902, April 16, 1999; and Hogan, B. L. M. (1996) Genes Dev. 10, 1580-1594.	Induction of Cartilage, Tissue and Bone Growth, and Diabetes

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
BMP-12	GeneSeq Accession R78734	WO9516035	BMP-12 belongs to the transforming growth factor-beta (TGFB) superfamily. Bone morphogenic protein induces bone formation.	BMP-12 activity can be determined using the following assays known in the art: Nat Genet. 2001 Jan; 27(1):84-8; Eur J Biochem 1996 Apr 1; 237(1):295-302; J Biol Chem, Vol. 274, Issue 16, 10897-10902, April 16, 1999; and Hogan, B. L. M. (1996) Genes Dev. 10, 1580-1594.	Induction of Cartilage, Tissue and Bone Growth, and Diabetes
BMP-15	GeneSeq Accession W11261	WO9636710	BMP-15 belongs to the transforming growth factor-beta (TGFB) superfamily. Bone morphogenic protein induces bone formation.	BMP-15 activity can be determined using the following assays known in the art: Nat Genet. 2001 Jan; 27(1):84-8; Eur J Biochem 1996 Apr 1; 237(1):295-302; J Biol Chem, Vol. 274, Issue 16, 10897-10902, April 16, 1999; and Hogan, B. L. M. (1996) Genes Dev. 10, 1580-1594.	Induction of Cartilage, Tissue and Bone Growth, and Diabetes
BMP-17	GeneSeq Accession Y17870	WO9929718	BMP-17 belongs to the transforming growth factor-beta (TGFB) superfamily. Bone morphogenic protein induces bone formation.	BMP-17 activity can be determined using the following assays known in the art: Nat Genet. 2001 Jan; 27(1):84-8; Eur J Biochem 1996 Apr 1; 237(1):295-302; J Biol Chem, Vol. 274, Issue 16, 10897-10902, April 16, 1999; and Hogan, B. L. M. (1996) Genes Dev. 10, 1580-1594.	Induction of Cartilage, Tissue and Bone Growth, and Diabetes
BMP-18	GeneSeq Accession Y17871	WO9929718	BMP-18 belongs to the transforming growth factor-beta (TGFB) superfamily. Bone morphogenic protein induces bone formation.	BMP-18 activity can be determined using the following assays known in the art: Nat Genet. 2001 Jan; 27(1):84-8; Eur J Biochem 1996 Apr 1; 237(1):295-302; J Biol Chem, Vol. 274, Issue 16, 10897-10902, April 16, 1999; and Hogan, B. L. M. (1996) Genes Dev. 10, 1580-1594.	Induction of Cartilage, Tissue and Bone Growth, and Diabetes

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
Inhibin alpha	GeneSeq Accession B02806	WO0020591	The inhibin beta A subunit joins the alpha subunit to form a pituitary FSH secretion inhibitor. Inhibin has been shown to regulate gonadal stromal cell proliferation negatively and to have tumour-suppressor activity. In addition, serum levels of inhibin have been shown to reflect the size of granulosa-cell tumors and can therefore be used as a marker for primary as well as recurrent disease.	Tumor suppressor activity of inhibin can be determined using assays known in the art: Matznuk et al., Nature 1992 Nov. 26: 360 (6402); 313-9.	Tumor suppression.
Inhibin beta	GeneSeq Accession H02808	WO0020591	The inhibin beta A subunit joins the alpha subunit to form a pituitary FSH secretion inhibitor. Inhibin has been shown to regulate gonadal stromal cell proliferation negatively and to have tumour-suppressor activity. In addition, serum levels of inhibin have been shown to reflect the size of granulosa-cell tumors and can therefore be used as a marker for primary as well as recurrent disease.	Tumor suppressor activity of inhibin can be determined using assays known in the art: Matznuk et al., Nature 1992 Nov. 26: 360 (6402); 313-9.	Tumor suppression.
Cerebus Protein	GeneSeq Accession W86032	WO9849296	Cerebus is believed to be involved in the inhibition of BMP activity	BMP activity, in the presence of the antagonist Cerebus, can be determined using the following assays known in the art: Nat Genet. 2001 Jan; 27(1):84-8; Eur J Biochem 1996 Apr 1; 237(1):295-302; J Biol Chem, Vol. 274, Issue 16, 10897-10902, April 16, 1999; and Hogan, B. L. M. (1996) Genes Dev. 10, 1580-1594.	BMP Antagonist useful for Osteosarcoma, abnormal bone growth.

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
Soluble BMP Receptor Kinase Protein-3	GeneSeq Accession R95227	WO9614579	Soluble BMP receptor kinase protein-3 is involved in the binding of BMPs. Soluble BMP receptor kinase protein-3 is useful as an antagonist for the inhibition of BMP activity.	BMP activity, in the presence of the soluble antagonist BMP receptor kinase protein-3, can be determined using the following assays known in the art: Nat Genet. 2001 Jan; 27(1):84-8; Eur J Biochem 1996 Apr 1; 237(1):295-302; J Biol Chem, Vol. 274, Issue 16, 10897-10902, April 16, 1999; and Hogan, B. L. M. (1996) Genes Dev. 10, 1580-1594.	BMP Antagonist useful for Osteosarcoma, abnormal bone growth.
BMP Processing Enzyme Furin	GeneSeq Accession W36099	WO9741250	BMPs belong to the transforming growth factor-beta (TGFB) superfamily. Bone morphogenic protein induces bone formation.	BMP activity, in the presence of the Furin, can be determined using the following assays known in the art: Nat Genet. 2001 Jan; 27(1):84-8; Eur J Biochem 1996 Apr 1; 237(1):295-302; J Biol Chem, Vol. 274, Issue 16, 10897-10902, April 16, 1999; and Hogan, B. L. M. (1996) Genes Dev. 10, 1580-1594.	Bone formation or Regeneration Abnormalities
TGF-beta I	GeneSeq Accession R29657	WO9216228	Members of the TGF-beta family of proteins initiate cell signaling by binding to heteromeric receptor complexes of type I (TbetaRI) and type II (TbetaRII) serine/threonine kinase receptors (reviewed by Massague, J. et al. (1994) Trends Cell Biol. 4:172-178; Miyazono, K. et al. (1994) Adv. Immunol. 55:181-220). Activation of this heteromeric receptor complex occurs when TGF-beta. binds to TbetaRII, which then recruits and phosphorylates TbetaRI. Activated TbetaRI then propagates the signal to downstream targets (Chen, F. and Weinberg, R.A. (1995) PNA892:1565-1569; Wrana, J. L. et al. (1994) Nature 370:341.	The effect of TGF betas on signaling can be assayed by treating Primary BAFs transfectected with a construct called p3TP-Lux, containing a TGF-beta responsive promoter fused to a reporter gene, and measuring luciferase gene expression (Wrana et al., 1994, Nature 370: 341-347).	Useful for treating cancer and to promote wound healing.

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
TGF-beta 2	GeneSeq Accession R39659	EP542679	<p>Members of the TGF-beta family of proteins initiate cell signaling by binding to heteromeric receptor complexes of type I (TbetaRI) and type II (TbetaRII) serine/threonine kinase receptors (reviewed by Massague, J. et al. (1994) Trends Cell Biol. 4:172-178; Miyazono, K. et al. (1994) Adv. Immunol. 55:181-220). Activation of this heteromeric receptor complex occurs when TGF-beta. binds to TbetaRII, which then recruits and phosphorylates TbetaRI. Activated TbetaRI then propagates the signal to downstream targets (Chen, F. and Weinberg, R.A. (1995) PNA892:1565-1569; Wrana, J. L. et al. (1994) Nature 370:341.</p>	<p>The effect of TGF betas on signaling can be assayed by treating Primary BAECs transfected with a construct called p3TP-Lux, containing a TGF-beta responsive promoter fused to a reporter gene, and measuring luciferase gene expression (Wrana et al., 1994, Nature 370: 341-347).</p>	Useful for treating cancer and to promote wound healing.
ZTGF-beta 9	GeneSeq Accession Y70654	WO0015798	<p>Members of the TGF-beta family of proteins initiate cell signaling by binding to heteromeric receptor complexes of type I (TbetaRI) and type II (TbetaRII) serine/threonine kinase receptors (reviewed by Massague, J. et al. (1994) Trends Cell Biol. 4:172-178; Miyazono, K. et al. (1994) Adv. Immunol. 55:181-220). Activation of this heteromeric receptor complex occurs when TGF-beta. binds to TbetaRII, which then recruits and phosphorylates TbetaRI. Activated TbetaRI then propagates the signal to downstream targets (Chen, F. and Weinberg, R.A. (1995) PNA892:1565-1569; Wrana, J. L. et al. (1994) Nature 370:341.</p>	<p>The effect of TGF betas on signaling can be assayed by treating Primary BAECs transfected with a construct called p3TP-Lux, containing a TGF-beta responsive promoter fused to a reporter gene, and measuring luciferase gene expression (Wrana et al., 1994, Nature 370: 341-347).</p>	Useful for treating cancer and to promote wound healing.

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication
Anti-TGF beta family antibodies		GB2305921	Members of the TGF-beta family of proteins initiate cell signaling by binding to heteromeric receptor complexes of type I (TbetaRI) and type II (TbetaRII) serine/threonine kinase receptors (reviewed by Massague, J. et al. (1994) Trends Cell Biol. 4:172-178; Miyazono, K. et al. (1994) Adv. Immunol. 55:181-220). Activation of this heteromeric receptor complex occurs when TGF-beta binds to TbetaRII, which then recruits and phosphorylates TbetaRI. Activated TbetaRI then propagates the signal to downstream targets (Chen, F. and Weinberg, R.A. (1995) PNA892:1565-1569; Wrana, J. L. et al. (1994) Nature 370:341).	The effect of TGF betas on signaling in the presence of an anti-TGF beta antibody, can be assayed by treating Primary BAEs transfected with a construct called p3TP-Lux, containing a TGF-beta responsive promoter fused to a reporter gene, and measuring luciferase gene expression (Wrana et al., 1994, Nature 370: 341-347).	Useful for control of fibrosis, immune, and inflammatory disease.
Latent TGF beta binding protein II	GeneSeq Accession Y70552	WO0012551	Members of the TGF-beta family of proteins initiate cell signaling by binding to heteromeric receptor complexes of type I (TbetaRI) and type II (TbetaRII) serine/threonine kinase receptors (reviewed by Massague, J. et al. (1994) Trends Cell Biol. 4:172-178; Miyazono, K. et al. (1994) Adv. Immunol. 55:181-220). Activation of this heteromeric receptor complex occurs when TGF-beta binds to TbetaRII, which then recruits and phosphorylates TbetaRI. Activated TbetaRI then propagates the signal to downstream targets (Chen, F. and Weinberg, R.A. (1995) PNA892:1565-1569; Wrana, J. L. et al. (1994) Nature 370:341).	The effect of TGF betas on signaling in the presence of a TGF beta binding protein, can be assayed by treating Primary BAEs transfected with a construct called p3TP-Lux, containing a TGF-beta responsive promoter fused to a reporter gene, and measuring luciferase gene expression (Wrana et al., 1994, Nature 370: 341-347).	Useful for inhibiting tissue or tumor growth.

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
MP52	GeneSeq Accession W36100	WO9741250	Members of the TGF-beta family of proteins initiate cell signaling by binding to heteromeric receptor complexes of type I (TbetaRI) and type II (TbetaRII) serine/threonine kinase receptors (reviewed by Massague, J. et al. (1994) Trends Cell Biol. 4:172-178; Miyazono, K. et al. (1994) Adv. Immunol. 55:181-220). Activation of this heteromeric receptor complex occurs when TGF-beta binds to TbetaRII, which then recruits and phosphorylates TbetaRI. Activated TbetaRI then propagates the signal to downstream targets (Chen, F. and Weinberg, R.A. (1995) PNA892:1565-1569; Wrana, J. L. et al. (1994) Nature 370:341.	The effect of TGF betas on signaling can be assayed by treating Primary BAECs transfected with a construct called p3TP-Lux, containing a TGF-beta responsive promoter fused to a reporter gene, and measuring luciferase gene expression (Wrana et al., 1994, Nature 370: 341-347).	Bone formation or Regeneration Abnormalities
b57 Protein	GeneSeq Accession W69293	WO9837195	BMPs are involved in the induction of bone formation. Specific antagonists are useful in preventing this activity from occurring.	BMP activity, in the presence of b57 protein, can be determined using the following assays known in the art: Nat Genet. 2001 Jan; 27(1):84-8; Eur J Biochem 1996 Apr 1; 237(1):295-302; J Biol Chem, Vol. 274, Issue 16, 1089-10902, April 16, 1999; and Hogan, B.L.M. (1996) Genes Deve. 10, 1580-1594.	BMP Antagonist useful for Osteosarcoma, abnormal bone growth.
Resistin	GeneSeq Accession W69293	WO0064920	This gene belongs to the family defined by mouse FIZZ1 and FIZZ3/Resistin genes. The characteristic feature of this family is the C-terminal stretch of 10 cys residues with identical spacing. The mouse homolog of this protein is secreted by adipocytes, may be the hormone potentially linking obesity to type II diabetes.	Ability of resistin to influence type II diabetes can be determined using assays known in the art: Pontoglio et al., J Clin Invest 1998 May 15; 101(10):2215-22.	Type II diabetes and Syndrome X.
Galectin-4	GeneSeq Accession W11841	WO9703190	Galectins are a family of carbohydrate-binding proteins characterized by an affinity for beta-galactoside containing glycoconjugates.	Ability of Galectin-4 polypeptides to bind lactose can be determined using assays known in the art: Wada, et al., J Biol Chem 1997 Feb 28; 272(9):6078-86.	Lactose intolerance.



Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
APM-I, ACRP-30; Famoxin	GeneSeq Accession Y71035	W00026363	ACRP30 gene is exclusively expressed in adipose tissue. ACRP30 is thought to increase fatty acid oxidation by muscle tissue.	Ability of ACRP30 polypeptides to influence obesity and fat oxidation can be determined using assays known in the art: Fruebis et al., Proc Natl Acad Sci USA 2001 Feb 13; 98(4):2005-10.	Obesity, Metabolic disorders, Lipid Metabolism; Hormone Secretion.
ACRP-30 Homologue; Complement Component Clq C	GeneSeq Accession B30234	W00063376	ACRP30 gene is exclusively expressed in adipose tissue. ACRP30 is thought to increase fatty acid oxidation by muscle tissue.	Ability of ACRP30 homologue polypeptides to influence obesity and fat oxidation can be determined using assays known in the art: Fruebis et al., Proc Natl Acad Sci USA 2001 Feb 13; 98(4):2005-10.	Obesity, Metabolic disorders, Lipid Metabolism; Hormone Secretion.
Calpain-10a	GeneSeq Accession Y79567	W00023603	Calpain is believed to play a role in insulin secretion and insulin activity, and therefore may be useful in the treatment of type II diabetes.	Ability of Calpain-10 to influence type II diabetes can be determined using assays known in the art: Pontoglio et al., J Clin Invest 1998 May 15; 101(10):2215-22.	Diabetes mellitus; Regulation of Insulin secretory response; Insulin mediated glucose transport disorders.
Calpain-10b	GeneSeq Accession Y79568	W00023603	Calpain is believed to play a role in insulin secretion and insulin activity, and therefore may be useful in the treatment of type II diabetes.	Ability of Calpain-10 to influence type II diabetes can be determined using assays known in the art: Pontoglio et al., J Clin Invest 1998 May 15; 101(10):2215-22.	Diabetes mellitus; Regulation of Insulin secretory response; Insulin mediated glucose transport disorders.
Calpain-10c	GeneSeq Accession Y79569	W00023603	Calpain is believed to play a role in insulin secretion and insulin activity, and therefore may be useful in the treatment of type II diabetes.	Ability of Calpain-10 to influence type II diabetes can be determined using assays known in the art: Pontoglio et al., J Clin Invest 1998 May 15; 101(10):2215-22.	Diabetes mellitus; Regulation of Insulin secretory response; Insulin mediated glucose transport disorders.
PDGF-D	GeneSeq Accession Y71130	W00027879	Vascular Endothelial Growth Factor.	Proliferation assay using NR6R-3T3 cells (Rizzino 1988 Cancer Res. 48: 4266).	Wound Healing; Atherosclerosis.
FasL	GeneSeq Accession Y28594	W09936079	Activities associated with apoptosis and immune system functions.	Activity can be determined using Apoptosis assays known in the art: Walczak et al. (1996) EMBOJ 16: 5386-5397.	Apoptosis-related disorders; Autoimmune disorders; Graft v-Host disorders.

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
Chondro modulin-like protein	GeneSeq Accession Y71262	W00029579	Chondromodulin proteins are cartilage proteins thought to confer resistance to angiogenesis, and thus are useful as anti-angiogenic agents that may have utility in combating cancer.	Ability of Chondromodulin-like protein to inhibit vascularization can be determined using assays known in the art: Hirakie et al., J Biol Chem 1997 Dec 19; 272(51):32419-26.	Antiangiogenic agent; Osteoblast proliferation stimulator; prevents vascularization of cartilage tissue; Useful to treat cancer.
Patched	GeneSeq Accession W72969	US5837538	Patched is a tumour-suppressor receptor for Sonic hedgehog (shh), which is a protein that controls developmental patterning and growth.	Ability of soluble Patched to bind to and inhibit the activities of shh can be determined using assays known in the art: Stone et al., Nature 1996 Nov 14; 384(6605):129-34.	Receptor for Hedgehog cellular proliferation signaling molecule. This receptor is useful as a means of preventing cellular proliferation via the shh signaling pathway, thus useful for cancers.
Patched-2	GeneSeq Accession Y43261	WO9953058	Patched is a tumour-suppressor receptor for Sonic hedgehog (shh), which is a protein that controls developmental patterning and growth.	Ability of soluble Patched to bind to and inhibit the activities of shh can be determined using assays known in the art: Stone et al., Nature 1996 Nov 14; 384(6605):129-34.	Receptor for Hedgehog cellular proliferation signaling molecule. This receptor is useful as a means of preventing cellular proliferation via the shh signaling pathway, thus useful for cancers.
Maspin; Protease Inhibitor 5	GeneSeq Accession R50938	WO9405804	Maspin is a member of the serpin family of serine protease inhibitors that is thought to suppress tumor metastasis.	The inhibitory effects of Maspin and other protease inhibitors can be assayed using methods known in the art such as a labeled protease substrate, for example, Universal Protease Substrate (casein, resorufin-labeled); Roche Molecular Biochemicals, Cat. No. 1080733.	Tumor suppressor which is down-regulated in breast cancers. The maspin protein has tumour suppressing and invasion suppressing activity.
Endostatin	GeneSeq Accession B28399	WO0064946	Endostatin is believed to inhibit effects of capillary endothelial cell proliferation.	The inhibitory effects of endostatin can be assayed using assays disclosed by Cao et al. (1996) J. Biol. Chem. 271 29461-29467.	Anti-angiogenic activity. Useful in the prevention and/or treatment of cancers.

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
aFGF; FGF-1	GeneSeq Accession P94037	EP298723	Fibroblast Growth Factor	Proliferation assay using NR6R-3T3 cells (Rizzino 1988 Cancer Res. 48: 4266); Examples 23 and 39 disclosed herein.	Promotion of growth and proliferation of cells, such as epithelial cells and keratinocytes. Antagonists may be useful as anti-cancer agents.
bFGF; FGF-2	GeneSeq Accession R06685	FR2642086	Fibroblast Growth Factor	Proliferation assay using NR6R-3T3 cells (Rizzino 1988 Cancer Res. 48: 4266); Examples 23 and 39 disclosed herein.	Promotion of growth and proliferation of cells, such as epithelial cells and keratinocytes. Antagonists may be useful as anti-cancer agents.
FGF-3; INT-2	GeneSeq Accession R07824	WO9503831	Fibroblast Growth Factor	Proliferation assay using NR6R-3T3 cells (Rizzino 1988 Cancer Res. 48: 4266); Examples 23 and 39 disclosed herein.	Promotion of growth and proliferation of cells, such as epithelial cells and keratinocytes. Antagonists may be useful as anti-cancer agents.
FGF-4; HST-1; HBGF-4	GeneSeq Accession R07825	WO9503831	Fibroblast Growth Factor	Proliferation assay using NR6R-3T3 cells (Rizzino 1988 Cancer Res. 48: 4266); Examples 23 and 39 disclosed herein.	Promotion of growth and proliferation of cells, such as epithelial cells and keratinocytes. Antagonists may be useful as anti-cancer agents.
FGF-5	GeneSeq Accession W22600	WO9730155	Fibroblast Growth Factor	Proliferation assay using NR6R-3T3 cells (Rizzino 1988 Cancer Res. 48: 4266); Examples 23 and 39 disclosed herein.	Promotion of growth and proliferation of cells, such as epithelial cells and keratinocytes. Antagonists may be useful as anti-cancer agents.
FGF-6; Heparin binding secreted transforming factor-2	GeneSeq Accession R58555	EP613946	Fibroblast Growth Factor	Proliferation assay using NR6R-3T3 cells (Rizzino 1988 Cancer Res. 48: 4266); Examples 23 and 39 disclosed herein.	Promotion of growth and proliferation of cells, such as epithelial cells and keratinocytes. Antagonists may be useful as anti-cancer agents.

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
FGF-8	GeneSeq Accession R80783	WO9524928	Fibroblast Growth Factor	Proliferation assay using NR6R-3T3 cells (Rizzino 1988 Cancer Res. 48: 4266); Examples 23 and 39 disclosed herein.	Promotion of growth and proliferation of cells, such as epithelial cells and keratinocytes. Antagonists may be useful as anti-cancer agents.
FGF-9; Gila activating factor	GeneSeq Accession R70822	WO9503831	Fibroblast Growth Factor	Proliferation assay using NR6R-3T3 cells (Rizzino 1988 Cancer Res. 48: 4266); Examples 23 and 39 disclosed herein.	Promotion of growth and proliferation of cells, such as epithelial cells and keratinocytes. Antagonists may be useful as anti-cancer agents.
FGF-12; Fibroblast growth factor homologous factor-1	GeneSeq Accession W06309	WO9635708	Fibroblast Growth Factor	Proliferation assay using NR6R-3T3 cells (Rizzino 1988 Cancer Res. 48: 4266); Examples 23 and 39 disclosed herein.	Promotion of growth and proliferation of cells, such as epithelial cells and keratinocytes. Antagonists may be useful as anti-cancer agents.
FGF-15	GeneSeq Accession Y08582	WO9927100	Fibroblast Growth Factor	Proliferation assay using NR6R-3T3 cells (Rizzino 1988 Cancer Res. 48: 4266); Examples 23 and 39 disclosed herein.	Promotion of growth and proliferation of cells, such as epithelial cells and keratinocytes. Antagonists may be useful as anti-cancer agents.
FGF-16	GeneSeq Accession Y05474	WO9918128	Fibroblast Growth Factor	Proliferation assay using NR6R-3T3 cells (Rizzino 1988 Cancer Res. 48: 4266); Examples 23 and 39 disclosed herein.	Promotion of growth and proliferation of cells, such as epithelial cells and keratinocytes. Antagonists may be useful as anti-cancer agents.
FGF-18	GeneSeq Accession Y08590	WO9927100	Fibroblast Growth Factor	Proliferation assay using NR6R-3T3 cells (Rizzino 1988 Cancer Res. 48: 4266); Examples 23 and 39 disclosed herein.	Promotion of growth and proliferation of cells, such as epithelial cells and keratinocytes. Antagonists may be useful as anti-cancer agents.

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
fit-3 ligand	GeneSeq Accession R67541	EP627487	Stem Cell Progenitor	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ.	Promotion of immune cell growth and/or differentiation.
VEGF-110	GeneSeq Accession Y69417	WO0013702	Promotes the growth and/or proliferation of endothelial cells.	VEGF activity can be determined using assays known in the art, such as those disclosed in International Publication No. WO0045835, for example.	Promotion of growth and proliferation of cells, such as vascular endothelial cells. Antagonists may be useful as anti-angiogenic agents, and may be applicable for cancer.
VEGB-121	GeneSeq Accession B50432	WO0071713	Promotes the growth and/or proliferation of endothelial cells.	VEGF activity can be determined using assays known in the art, such as those disclosed in International Publication No. WO0045835, for example.	Promotion of growth and proliferation of cells, such as vascular endothelial cells. Antagonists may be useful as anti-angiogenic agents, and may be applicable for cancer.
VEGF-138	GeneSeq Accession Y43483	WO9940197	Promotes the growth and/or proliferation of endothelial cells.	VEGF activity can be determined using assays known in the art, such as those disclosed in International Publication No. WO0045835, for example.	Promotion of growth and proliferation of cells, such as vascular endothelial cells. Antagonists may be useful as anti-angiogenic agents, and may be applicable for cancer.
VEGF-145	GeneSeq Accession Y69413	WO0013702	Promotes the growth and/or proliferation of endothelial cells.	VEGF activity can be determined using assays known in the art, such as those disclosed in International Publication No. WO0045835, for example.	Promotion of growth and proliferation of cells, such as vascular endothelial cells. Antagonists may be useful as anti-angiogenic agents, and may be applicable for cancer.

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
VEGF-162	GeneSeq Accession Y43484	W09940197	Promotes the growth and/or proliferation of endothelial cells.	VEGF activity can be determined using assays known in the art, such as those disclosed in International Publication No. WO0045835, for example.	Promotion of growth and proliferation of cells, such as vascular endothelial cells. Antagonists may be useful as anti-angiogenic agents, and may be applicable for cancer.
VEGF-165	GeneSeq Accession Y69414	WO0013702	Promotes the growth and/or proliferation of endothelial cells.	VEGF activity can be determined using assays known in the art, such as those disclosed in International Publication No. WO0045835, for example.	Promotion of growth and proliferation of cells, such as vascular endothelial cells. Antagonists may be useful as anti-angiogenic agents, and may be applicable for cancer.
VEGF-182	GeneSeq Accession Y43483	W09940197	Promotes the growth and/or proliferation of endothelial cells.	VEGF activity can be determined using assays known in the art, such as those disclosed in International Publication No. WO0045835, for example.	Promotion of growth and proliferation of cells, such as vascular endothelial cells. Antagonists may be useful as anti-angiogenic agents, and may be applicable for cancer.
VEGF-189	GeneSeq Accession Y69415	WO0013702	Promotes the growth and/or proliferation of endothelial cells.	VEGF activity can be determined using assays known in the art, such as those disclosed in International Publication No. WO0045835, for example.	Promotion of growth and proliferation of cells, such as vascular endothelial cells. Antagonists may be useful as anti-angiogenic agents, and may be applicable for cancer.
VEGF-206	GeneSeq Accession Y69416	W00013702	Promotes the growth and/or proliferation of endothelial cells.	VEGF activity can be determined using assays known in the art, such as those disclosed in International Publication No. WO0045835, for example.	Promotion of growth and proliferation of cells, such as vascular endothelial cells. Antagonists may be useful as anti-angiogenic agents, and may be applicable for cancer.
VEGF-D	GeneSeq Accession W53240	WO9807832	Promotes the growth and/or proliferation of endothelial cells.	VEGF activity can be determined using assays known in the art, such as those disclosed in International Publication No. WO0045835, for example.	Promotion of growth and proliferation of cells, such as vascular endothelial cells. Antagonists may be useful as anti-angiogenic agents, and may be applicable for cancer.

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
VEGF-E, VEGF-X	GeneSeq Accession Y33679	WO9947677	Promotes the growth and/or proliferation of endothelial cells.	VEGF activity can be determined using assays known in the art, such as those disclosed in International Publication No. WO0045835, for example.	Promotion of growth and proliferation of cells, such as vascular endothelial cells. Antagonists may be useful as anti-angiogenic agents, and may be applicable for cancer.
VEGF Receptor; KDR; flk-1	GeneSeq Accession W69679	WO9831794	Receptor for VEGF polypeptides	VEGF activity, in the presence of flk-1 polypeptides, can be determined using assays known in the art, such as those disclosed in International Publication No. WO0045835, for example.	VEGF Receptor. Fusion protein with the extracellular domain is useful as an anti-angiogenic agent. Antagonists may be useful in the promotion of angiogenesis.
Soluble VEGF Receptor	GeneSeq Accession W47037	US5712380	Receptor for VEGF polypeptides	VEGF activity, in the presence of VEGF Receptor polypeptides, can be determined using assays known in the art, such as those disclosed in International Publication No. WO0045835, for example.	VEGF Receptor. Fusion protein with the extracellular domain is useful as an anti-angiogenic agent. Antagonists may be useful in the promotion of angiogenesis.
flt-1	GeneSeq Accession Y70751	WO0021560	Receptor for VEGF polypeptides	VEGF activity, in the presence of flt-1 polypeptides, can be determined using assays known in the art, such as those disclosed in International Publication No. WO0045835, for example.	VEGF Receptor. Fusion protein with the extracellular domain is useful as an anti-angiogenic agent. Antagonists may be useful in the promotion of angiogenesis.
VEGF R-3; flt-4	GeneSeq Accession B29047	WO0058511	Receptor for VEGF polypeptides	VEGF activity, in the presence of flt-4 polypeptides, can be determined using assays known in the art, such as those disclosed in International Publication No. WO0045835, for example.	VEGF Receptor. Fusion protein with the extracellular domain is useful as an anti-angiogenic agent. Antagonists may be useful in the promotion of angiogenesis.
Neuropilin-1	GeneSeq Accession Y06319	WO9929858	Vascular Endothelial Growth Factor	VEGF activity can be determined using assays known in the art, such as those disclosed in International Publication No. WO0045835, for example.	Promotion of growth and proliferation of cells, such as vascular endothelial cells. Antagonists may be useful as anti-angiogenic agents, and may be applicable for cancer.

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
Neuropilin-2	GeneSeq Accession Y03618	WO9929858	Vascular Endothelial Growth Factor	VEGF activity can be determined using assays known in the art, such as those disclosed in International Publication No. WO0045835, for example.	Promotion of growth and proliferation of cells, such as vascular endothelial cells. Antagonists may be useful as anti-angiogenic agents, and may be applicable for cancer.
Human fast twitch skeletal muscle troponin C	GeneSeq Accession W22597	W09730085	Troponins are contractile proteins that are thought to inhibit angiogenesis. High levels may contribute to the difficulty encountered in revascularizing the ischemic myocardium after cardiovascular injury.	Ability of soluble Troponins to inhibit angiogenesis can be determined using assays known in the art. Proc Natl Acad Sci U S A 1999 Mar 16;96(6):2645-50.	Anti-angiogenesis
Human fast twitch skeletal muscle troponin I	GeneSeq Accession W18054	W09730085	Troponins are contractile proteins that are thought to inhibit angiogenesis. High levels may contribute to the difficulty encountered in revascularizing the ischemic myocardium after cardiovascular injury.	Ability of soluble Troponins to inhibit angiogenesis can be determined using assays known in the art. Proc Natl Acad Sci U S A 1999 Mar 16;96(6):2645-50.	Anti-angiogenesis
Human fast twitch skeletal muscle troponin T	GeneSeq Accession W22599	W09730085	Troponins are contractile proteins that are thought to inhibit angiogenesis. High levels may contribute to the difficulty encountered in revascularizing the ischemic myocardium after cardiovascular injury.	Ability of soluble Troponins to inhibit angiogenesis can be determined using assays known in the art. Proc Natl Acad Sci U S A 1999 Mar 16;96(6):2645-50.	Anti-angiogenesis
fragment. myofibrillar protein troponin I	GeneSeq Accession W18053	W09719955	Troponins are contractile proteins that are thought to inhibit angiogenesis. High levels may contribute to the difficulty encountered in revascularizing the ischemic myocardium after cardiovascular injury.	Ability of soluble Troponins to inhibit angiogenesis can be determined using assays known in the art. Proc Natl Acad Sci U S A 1999 Mar 16;96(6):2645-50.	Anti-angiogenesis
myofibrillar protein troponin I	GeneSeq Accession W18054	W09719955	Troponins are contractile proteins that are thought to inhibit angiogenesis. High levels may contribute to the difficulty encountered in revascularizing the ischemic myocardium after cardiovascular injury.	Ability of soluble Troponins to inhibit angiogenesis can be determined using assays known in the art. Proc Natl Acad Sci U S A 1999 Mar 16;96(6):2645-50.	Anti-angiogenesis



Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
Troponin peptides	GeneSeq Accessions Y29581, Y29582, Y29583, Y29584, Y29585, and Y29586	WO9933874	Troponins are contractile proteins that are thought to inhibit angiogenesis. High levels may contribute to the difficulty encountered in revascularizing the ischemic myocardium after cardiovascular injury.	Ability of soluble Troponins to inhibit angiogenesis can be determined using assays known in the art. Proc Natl Acad Sci U S A 1999 Mar 16;96(6):2645-50.	Anti-angiogenesis
Human fast twitch skeletal muscle Troponin subunit C	GeneSeq Accession B00134	WO0054770	Troponins are contractile proteins that are thought to inhibit angiogenesis. High levels may contribute to the difficulty encountered in revascularizing the ischemic myocardium after cardiovascular injury.	Ability of soluble Troponins to inhibit angiogenesis can be determined using assays known in the art. Proc Natl Acad Sci U S A 1999 Mar 16;96(6):2645-50.	Anti-angiogenesis
Human fast twitch skeletal muscle Troponin subunit I Protein	GeneSeq Accession B00135	WO0054770	Troponins are contractile proteins that are thought to inhibit angiogenesis. High levels may contribute to the difficulty encountered in revascularizing the ischemic myocardium after cardiovascular injury.	Ability of soluble Troponins to inhibit angiogenesis can be determined using assays known in the art. Proc Natl Acad Sci U S A 1999 Mar 16;96(6):2645-50.	Anti-angiogenesis
Human fast twitch skeletal muscle Troponin subunit T	GeneSeq Accession B00136	WO0054770	Troponins are contractile proteins that are thought to inhibit angiogenesis. High levels may contribute to the difficulty encountered in revascularizing the ischemic myocardium after cardiovascular injury.	Ability of soluble Troponins to inhibit angiogenesis can be determined using assays known in the art. Proc Natl Acad Sci U S A 1999 Mar 16;96(6):2645-50.	Anti-angiogenesis
Activator Inhibitor-1; PAI-1	GeneSeq Accession R08411	WO9013648	PAIs are believed to play a role in cancer, and cardiovascular disease and blood-clotting disorders.	Methods that measure plasminogen activator inhibitor (PAI) activity are known in the art, for example, assay the ability of PAI to inhibit tissue plasminogen activator (tPA) or urokinase (uPA): J Biochem Biophys Methods 2000 Sep 11; 45(2):127-40, Breast Cancer Res Treat 1996;41(2):141-6. Methods that measure anti-angiogenesis activity are known in the art, for example, Proc Natl Acad Sci U S A 1999 Mar 16; 96(6):2645-50.	Anti-angiogenesis; blood-clotting disorders.

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
Plasminogen Activator Inhibitor-2; PAI-2	GeneSeq Accession P94160	DE3722673	PAIs are believed to play a role in cancer, and cardiovascular disease and blood-clotting disorders.	Methods that measure plasminogen activator inhibitor (PAI) activity are known in the art, for example, assay the ability of PAI to inhibit tissue plasminogen activator (tPA) or urokinase (uPA): J Biochem Biophys Methods 2000 Sep 11; 45(2):127-40, Breast Cancer Res Treat 1996;41(2):141-6. Methods that measure anti-angiogenesis activity are known in the art, for example, Proc Natl Acad Sci U S A 1999 Mar 16; 96(6):2645-50.	Anti-angiogenesis; blood-clotting disorders.
Activator Inhibitor-2; PAI-2	GeneSeq Accession R10921	WO9102057	PAIs are believed to play a role in cancer, and cardiovascular disease and blood-clotting disorders.	Methods that measure plasminogen activator inhibitor (PAI) activity are known in the art, for example, assay the ability of PAI to inhibit tissue plasminogen activator (tPA) or urokinase (uPA): J Biochem Biophys Methods 2000 Sep 11; 45(2):127-40, Breast Cancer Res Treat 1996;41(2):141-6. Methods that measure anti-angiogenesis activity are known in the art, for example, Proc Natl Acad Sci U S A 1999 Mar 16; 96(6):2645-50.	Anti-angiogenesis; blood-clotting disorders.

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
Human PAI-1 mutants	GeneSeq Accessions R11755, R11756, R11757, R11758, R11759, R11760, R11761, R11762 and R11763	WO9105048	PAIs are believed to play a role in cancer, and cardiovascular disease and blood-clotting disorders.	Methods that measure plasminogen activator inhibitor (PAI) activity are known in the art, for example, assay the ability of PAI to inhibit tissue plasminogen activator (tPA) or urokinase (uPA): J Biochem Biophys Methods 2000 Sep 11; 45(2):127-40, Breast Cancer Res Treat 1996;41(2):141-6. Methods that measure anti-angiogenesis activity are known in the art, for example, Proc Natl Acad Sci U S A 1999 Mar 16; 96(6):2645-50.	Anti-angiogenesis; blood-clotting disorders.
CXCR3, CXCR3	GeneSeq Accession Y79372	WO0018431	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein coupled receptors. Over 40 human chemokines have been described, which bind to ~17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ.	Soluble CXCR3 polypeptides may be useful for inhibiting chemokine activities and viral infection.

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
Modified Rantes	GeneSeq Accession W38129	WO9737005	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein coupled receptors. Over 40 human chemokines have been described, which bind to ~17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ.	Immune disorders.
RANTES	GeneSeq Accession Y05299	EP905240	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein coupled receptors. Over 40 human chemokines have been described, which bind to ~17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ.	Immune disorders.

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication
MCL-1a	GeneSeq Accession R73914	WO9509232	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein coupled receptors. Over 40 human chemokines have been described, which bind to ~17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ.	Immune disorders.
MCP-1b	GeneSeq Accession Y26176	WO9929728	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein coupled receptors. Over 40 human chemokines have been described, which bind to ~17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ.	Immune disorders.

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
MCP-1 receptor	GeneSeq Accession R79165	WO9519436	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein coupled receptors. Over 40 human chemokines have been described, which bind to ~17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ.	Soluble MCP-1 Receptor polypeptides may be useful for inhibiting chemokine activities and viral infection.
MCP-3	GeneSeq Accession R73915	W09509232	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein coupled receptors. Over 40 human chemokines have been described, which bind to ~17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ.	Immune disorders.

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
MCP-4 receptor	GeneSeq Accession W56689	W09809171	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein coupled receptors. Over 40 human chemokines have been described, which bind to ~17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ.	Soluble MCP-4 Receptor polypeptides may be useful for inhibiting chemokine activities and viral infection.
RANTES receptor	GeneSeq Accession W29588	US5652133	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein coupled receptors. Over 40 human chemokines have been described, which bind to ~17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ.	Soluble RANTES Receptor polypeptides may be useful for inhibiting chemokine activities and viral infection.

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
CCR5 variant	GeneSeq Accession W88238	WO9854317	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein coupled receptors. Over 40 human chemokines have been described, which bind to ~17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ.	Soluble CCR5 polypeptides may be useful for inhibiting chemokine activities and viral infection.
CCR7	GeneSeq Accession B50859	US6153441	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein coupled receptors. Over 40 human chemokines have been described, which bind to ~17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ.	Soluble CCR7 polypeptides may be useful for inhibiting chemokine activities and viral infection.



Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
CXC3	GeneSeq Accession W23345	WO9727299	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein coupled receptors. Over 40 human chemokines have been described, which bind to ~17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ.	Immune disorders.
Eotaxin	GeneSeq Accession W10099	WO9700960	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein coupled receptors. Over 40 human chemokines have been described, which bind to ~17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ.	Immune disorders.
Neurotactin	GeneSeq Accessions Y77537, W34307, Y53259, and, Y77539	US6013257 WO9742224	Neurotactin may play a role in chemotactic leukocyte migration and brain inflammation processes.	Chemotactic leukocyte migration assays are known in the art, for example: J. Immunol. Methods 33, ((1980)); Nature 1997 Jun 5; 387(6633):611-7.	Immune disorders.

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
Human CK $\beta$ -9	GeneSeq Accession B50860	US6153441	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein coupled receptors. Over 40 human chemokines have been described, which bind to ~17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ.	Immune disorders.
Lymphotactin	GeneSeq Accession B50052	WO0073320	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ.	Immune disorders.
MIP-3 alpha	GeneSeq Accession W44398	WO9801557	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ.	Immune disorders.

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
MIP-3 beta	GeneSeq Accession W44399	WO9801557	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ.	Immune disorders.
MIP-Gamma	GeneSeq Accession R70798	WO9504158	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ.	Immune disorders.
Stem Cell Inhibitory Factor	GeneSeq Accession R11553	WO9104274	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ.	Hematopoietic growth factors.
thrombopoietin	GeneSeq Accession R79905	WO9521920	Thrombopoietin is involved in the regulation of the growth and differentiation of megakaryocytes and precursors thereof.	Thrombopoietin (TPO) can be assayed to determine regulation of growth and differentiation of megakaryocytes. Mol Cell Biol 2001 Apr; 21(8):2659-70; Exp Hematol 2001 Jan; 29(1):51-8 and within.	Hematopoietic growth factors.

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
c-kit ligand; SCF; Mast cell growth factor; MGF; Fibrosarcoma-derived stem cell factor	GeneSeq Accession Y53284, R83978 and R83977	EP992579 and EP676470	C-kit ligand is thought to stimulate the proliferation of mast cells, and is able to augment the proliferation of both myeloid and lymphoid hematopoietic progenitors in bone marrow culture. C-kit ligand is also thought to act synergistically with other cytokines.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ.	Hematopoietic growth factors.
Platelet derived growth factor	GeneSeq Accession B48653	WO0066736	Vascular Endothelial Growth Factor	VEGF activity can be determined using assays known in the art, such as those disclosed in International Publication No. WO0045835, for example.	Promotion of growth and proliferation of cells, such as vascular endothelial cells. Antagonists may be useful as anti-angiogenic agents, and may be applicable for cancer.
Melanoma inhibiting protein	GeneSeq Accession R69811	WO9503328	Melanoma inhibiting protein has melanoma-inhibiting activity and can be used to treat cancer (melanoma, glioblastoma, neuroblastoma, small cell lung cancer, neuroectodermal tumors) or as an immunosuppressant (it inhibits IL-2 or phytohaemagglutinin induced proliferation of peripheral blood lymphocytes).	Tumor suppressor activity of melanoma inhibiting protein can be determined using assays known in the art: Matzuk et al., Nature 1992 Nov 26;360(6402):313-9.	Cancer; melanoma
Glioma-derived growth factor	GeneSeq Accession R08120	EP399816	Vascular Endothelial Growth Factor	VEGF activity can be determined using assays known in the art, such as those disclosed in International Publication No. WO0045835, for example.	Promotion of growth and proliferation of cells, such as vascular endothelial cells. Antagonists may be useful as anti-angiogenic agents, and may be applicable for cancer.
Platelet derived growth factor precursor A	GeneSeq Accession R84759	EP682110	Vascular Endothelial Growth Factor	VEGF activity can be determined using assays known in the art, such as those disclosed in International Publication No. WO0045835, for example.	Promotion of growth and proliferation of cells, such as vascular endothelial cells. Antagonists may be useful as anti-angiogenic agents, and may be applicable for cancer.

<b>Therapeutic Protein X</b>	<b>Exemplary Identifier</b>	<b>PCT/Patent Reference</b>	<b>Biological Activity</b>	<b>Exemplary Activity Assay</b>	<b>Preferred Indication Y</b>
Platelet derived growth factor precursor B	GeneSeq Accession R84760	EP682110	Vascular Endothelial Growth Factor	VEGF activity can be determined using assays known in the art, such as those disclosed in International Publication No. WO0045835, for example.	Promotion of growth and proliferation of cells, such as vascular endothelial cells. Antagonists may be useful as anti-angiogenic agents, and may be applicable for cancer.
Platelet derived growth factor Bv-sis	GeneSeq Accession P80595 and P80596	EP282317	Vascular Endothelial Growth Factor	VEGF activity can be determined using assays known in the art, such as those disclosed in International Publication No. WO0045835, for example.	Promotion of growth and proliferation of cells, such as vascular endothelial cells. Antagonists may be useful as anti-angiogenic agents, and may be applicable for cancer.
Placental Growth Factor	GeneSeq Accessions R23059 and R23060	WO9206194	Vascular Endothelial Growth Factor	VEGF activity can be determined using assays known in the art, such as those disclosed in International Publication No. WO0045835, for example.	Promotion of growth and proliferation of cells, such as vascular endothelial cells. Antagonists may be useful as anti-angiogenic agents, and may be applicable for cancer.
Placental Growth Factor-2	GeneSeq Accession Y08289	DE19748734	Vascular Endothelial Growth Factor	VEGF activity can be determined using assays known in the art, such as those disclosed in International Publication No. WO0045835, for example.	Promotion of growth and proliferation of cells, such as vascular endothelial cells. Antagonists may be useful as anti-angiogenic agents, and may be applicable for cancer.
Thrombopoietin derivative1	GeneSeq Accession Y77244	WO0000612	Thrombopoietin is involved in the regulation of the growth and differentiation of megakaryocytes and precursors thereof.	Thrombopoietin (TPO) can be assayed to determine regulation of growth and differentiation of megakaryocytes. Mol Cell Biol 2001 Apr; 21(8):2659-70; Exp Hematol 2001 Jan; 29(1):51-8 and within.	Thrombocytopenia, cancer.

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
Thrombopoietin derivative2	GeneSeq Accession Y77255	WO00000612	Thrombopoietin is involved in the regulation of the growth and differentiation of megakaryocytes and preceptors thereof.	Thrombopoietin (TPO) can be assayed to determine regulation of growth and differentiation of megakaryocytes. Mol Cell Biol 2001 Apr; 21(8):2659-70; Exp Hematol 2001 Jan; 29(1):51-8 and within.	Thrombocytopenia, cancer.
Thrombopoietin derivative3	GeneSeq Accession Y77262	WO00000612	Thrombopoietin is involved in the regulation of the growth and differentiation of megakaryocytes and preceptors thereof.	Thrombopoietin (TPO) can be assayed to determine regulation of growth and differentiation of megakaryocytes. Mol Cell Biol 2001 Apr; 21(8):2659-70; Exp Hematol 2001 Jan; 29(1):51-8 and within.	Thrombocytopenia, cancer.
Thrombopoietin derivative4	GeneSeq Accession Y77267	WO00000612	Thrombopoietin is involved in the regulation of the growth and differentiation of megakaryocytes and preceptors thereof.	Thrombopoietin (TPO) can be assayed to determine regulation of growth and differentiation of megakaryocytes. Mol Cell Biol 2001 Apr; 21(8):2659-70; Exp Hematol 2001 Jan; 29(1):51-8 and within.	Thrombocytopenia, cancer.
Thrombopoietin derivative5	GeneSeq Accession Y77246	WO00000612	Thrombopoietin is involved in the regulation of the growth and differentiation of megakaryocytes and preceptors thereof.	Thrombopoietin (TPO) can be assayed to determine regulation of growth and differentiation of megakaryocytes. Mol Cell Biol 2001 Apr; 21(8):2659-70; Exp Hematol 2001 Jan; 29(1):51-8 and within.	Thrombocytopenia, cancer.
Thrombopoietin derivative6	GeneSeq Accession Y77253	WO00000612	Thrombopoietin is involved in the regulation of the growth and differentiation of megakaryocytes and preceptors thereof.	Thrombopoietin (TPO) can be assayed to determine regulation of growth and differentiation of megakaryocytes. Mol Cell Biol 2001 Apr; 21(8):2659-70; Exp Hematol 2001 Jan; 29(1):51-8 and within.	Thrombocytopenia, cancer.

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
Thrombopoietin derivative <sup>7</sup>	GeneSeq Accession Y77256	WO0000612	Thrombopoietin is involved in the regulation of the growth and differentiation of megakaryocytes and precursors thereof.	Thrombopoietin (TPO) can be assayed to determine regulation of growth and differentiation of megakaryocytes. Mol Cell Biol 2001 Apr; 21(8):2659-70; Exp Hematol 2001 Jan; 29(1):51-8 and within.	Thrombocytopenia, cancer.
Fractalkine	GeneSeq Accession Y53255	US6043086	Fractalkine is believed to play a role in chemotactic leukocyte migration and neurological disorders.	Fractalkine activity can be determined using Chemotactic leukocyte migration assays known in the art, for example: J. Immunol. Methods 33, ((1980)); Nature 1997 Jun 5;387(6633):611-7.	Immune disorders.
CXC3	GeneSeq Accession W23345	WO9757599	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein coupled receptors. Over 40 human chemokines have been described, which bind to ~17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ.	Immune disorders.

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
CCR7	GeneSeq Accession B50859	US6153441	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein coupled receptors. Over 40 human chemokines have been described, which bind to ~17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ.	Soluble CCR7 polypeptides may be useful for inhibiting chemokine activities and viral infection.
Nerve Growth Factor-beta	GeneSeq Accession R11474	EP414151	Nerve Growth Factor	Proliferation assay using NR6R-3T3 cells (Rizzino 1988 Cancer Res. 48: 4266)	Neurological disorders, cancer
Nerve Growth Factor-beta2	GeneSeq Accession W69725	EP859056	Nerve Growth Factor	Proliferation assay using NR6R 3T3 cells (Rizzino 1988 Cancer Res. 48: 4266)	Neurological disorders, cancer
Neurotrophin-3	GeneSeq Accession W8889	WO9821234	Neurotrophins regulate neuronal cell survival and synaptic plasticity.	Trk tyrosine kinase activation assays known in the art can be used to assay for neurotrophin activity, for example, Proc Natl Acad Sci U S A 2001 Mar 13;98(6):3555-3560.	Neurological disorders, cancer
Neurotrophin-3	GeneSeq Accession R47100	WO9325684	Neurotrophins regulate neuronal cell survival and synaptic plasticity.	Trk tyrosine kinase activation assays known in the art can be used to assay for neurotrophin activity, for example, Proc Natl Acad Sci U S A 2001 Mar 13;98(6):3555-3560.	Neurological disorders, cancer
Neurotrophin-4a	GeneSeq Accession R47101	WO9325684	Neurotrophins regulate neuronal cell survival and synaptic plasticity.	Trk tyrosine kinase activation assays known in the art can be used to assay for neurotrophin activity, for example, Proc Natl Acad Sci U S A 2001 Mar 13;98(6):3555-3560.	Neurological disorders, cancer



Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
Neurotrophin-4b	GeneSeq Accession R47102	WO9325684	Neurotrophins regulate neuronal cell survival and synaptic plasticity. tyrosine kinases.	Trk tyrosine kinase activation assays known in the art can be used to assay for neurotrophin activity, for example, Proc Natl Acad Sci U S A 2001 Mar 13;98(6):3555-3560.	Neurological disorders, cancer
Neurotrophin-4c	GeneSeq Accession R47103	WO9325684	Neurotrophins regulate neuronal cell survival and synaptic plasticity. tyrosine kinases.	Trk tyrosine kinase activation assays known in the art can be used to assay for neurotrophin activity, for example, Proc Natl Acad Sci U S A 2001 Mar 13;98(6):3555-3560.	Neurological disorders, cancer
Neurotrophin-4d	GeneSeq Accession R47102	WO9325684	Neurotrophins regulate neuronal cell survival and synaptic plasticity. tyrosine kinases.	Trk tyrosine kinase activation assays known in the art can be used to assay for neurotrophin activity, for example, Proc Natl Acad Sci U S A 2001 Mar 13;98(6):3555-3560.	Neurological disorders, cancer
Platelet-Derived Growth Factor A chain	GeneSeq Accession R38918	US5219739	Vascular Endothelial Growth Factor	VEGF activity can be determined using assays known in the art, such as those disclosed in International Publication No. W00045835, for example.	Promotion of growth and proliferation of cells, such as vascular endothelial cells. Hematopoietic and immune disorders. Antagonists may be useful as anti-angiogenic agents, and may be applicable for cancer
Platelet-Derived Growth Factor B chain	GeneSeq Accession R38919	US5219739	Vascular Endothelial Growth Factor	VEGF activity can be determined using assays known in the art, such as those disclosed in International Publication No. W00045835, for example.	Promotion of growth and proliferation of cells, such as vascular endothelial cells. Hematopoietic and immune disorders. Antagonists may be useful as anti-angiogenic agents, and may be applicable for cancer
Stromal Derived Factor-1 alpha	GeneSeq Accession Y39995	WO9948528	Stromal Growth Factor	Proliferation assay using NR6R-3T3 cells (Rizzino 1988 Cancer Res. 48: 4266)	Hematopoietic, immune disorders, cancer
Stromal Derived Factor-1 beta	GeneSeq Accession R75420	CA2117953	Stromal Growth Factor	Proliferation assay using NR6R-3T3 cells (Rizzino 1988 Cancer Res. 48: 4266)	Hematopoietic, immune disorders, cancer

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
Tarc	GeneSeq Accession W14917	WO9711969	Chemotactic for T lymphocytes. May play a role in T-cell development. Thought to bind CCR8 and CCR4	Chemotactic leukocyte migration assays are known in the art, for example: J. Immunol. Methods 33 (1980))	Antiinflammatory. Immune disorders, cancer
Prolactin	GeneSeq Accession R78691	WO9521625	Prolactin is involved in immune cell proliferation and apoptosis.	Immune cell proliferation and suppression of apoptosis by prolactin can be assayed by methods well-known in the art, for example, Buckley, AR and Buckley DJ, Ann N Y Acad Sci 2000; 917:522-33, and within.	Reproductive system disorders, cancer.
Prolactin2	GeneSeq Accession Y31764	US5955346	Prolactin is involved in immune cell proliferation and apoptosis.	Immune cell proliferation and suppression of apoptosis by prolactin can be assayed by methods well-known in the art, for example, Buckley, AR and Buckley DJ, Ann N Y Acad Sci 2000; 917:522-33, and within.	Reproductive system disorders, cancer.
Follicle stimulating hormone Alpha subunit	GeneSeq Accession Y54160	EP974359	FSH stimulates secretion of interleukin-1 by cells isolated from women in the follicular phase	FSH activities can be determined using assays known in the art; J Gend Specif Med 1999 Nov-Dec;2(6):30-4; Mol Cell Endocrinol. 1997 Nov 15;134(2):109-18.	Reproductive system disorders, cancer.
Follicle stimulating hormone Beta subunit	GeneSeq Accession Y54161	EP974359	FSH stimulates secretion of interleukin-1 by cells isolated from women in the follicular phase	FSH activities can be determined using assays known in the art; J Gend Specif Med 1999 Nov-Dec;2(6):30-4; Mol Cell Endocrinol. 1997 Nov 15;134(2):109-18.	Reproductive system disorders, cancer.

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
Substance P (tachykinin)	GeneSeq Accession B23027	WO0054053	Substance P is associated with immunoregulation.	Immunoregulation and bone marrow, cell proliferation by substance P can be assayed by methods well-known in the art, for example, Lai et al. Proc Natl Acad Sci USA 2001 Mar 27; 98(7):3970-5; Jallat-Daloz et al. Allergy Asthma Proc 2001 Jan-Feb; 22(1):17-23; Kahler et al. Exp Lung Res 2001 Jan-Feb; 27(1):25-46; and Adamus MA and Dabrowski ZJ. J Cell Biochem 2001; 81(3):499-506.	diabetes mellitus, hypertension, cancer
Oxytocin (Neurophysin I)	GeneSeq Accession B24085 and B24086	WO0053755	Oxytocin is involved in the induction of prostaglandin (E2) release as well as an increased amount of calcium release by smooth muscle cells.	Oxytocin and prostaglandin E(2) release and Oxytocin (Ca2+) increase can be assayed by methods well-known in the art, for example, Pavan et al., AM J Obstet Gynecol 2000 Jul; 183(1):76-82 and Holda et al., Cell Calcium 1996 Jul;20(1):43-51.	inflammatory disorders immunologic disorders, cancer
Vasopressin (Neurophysin II)	GeneSeq Accession B24085 and B24086	WO0053755	Vasopressin is believed to have a direct antidiuretic action on the kidney, and it is thought to cause vasoconstriction of the peripheral vessels.	Vasopressin activity can be determined using assays known in the art, for example, Endocr Regul 1996 Mar;30(1):13-17.	inflammatory disorders immunologic disorders, cancer
IL-1	GeneSeq Accession P60326	EP165654	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art. Matthews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Orencole & Dinarello (1989) Cytokine 1, 14-20.	inflammatory disorders, immunologic disorders, cancer

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
IL-1 mature	GeneSeq Accession R14855	EP456332	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Matthews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Orencole & Dinarello (1989) Cytokine 1, 14-20.	inflammatory disorders, immunologic disorders, cancer
IL-1 beta	GeneSeq Accession Y08322	WO9922763	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Matthews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Orencole & Dinarello (1989) Cytokine 1, 14-20.	inflammatory disorders, immunologic disorders, cancer
IL-3 variants	GeneSeq Accession P80382, P80383, P80384, and P80381	WO8806161	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Matthews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Kitamura et al (1989) J Cell Physiol. 140 323-334.	inflammatory disorders, immunologic disorders, cancer
IL-4	GeneSeq Accession P70615	WO8702990	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Matthews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Siegel & Mostowski (1990) J Immunol Methods 132,287-295.	inflammatory disorders, immunologic disorders, cancer

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
IL-4 muteins	GeneSeq Accession W52151 W52152 W52153 W52154 W52155 W52156 W52157 W52158 W52159 W52160 W52161 W52162 W52163 W52164 and W52165	WO9747744	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Matthews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Siegel & Mostowski (1990) <i>J Immunol Methods</i> 132,287-295.	inflammatory disorders, immunologic disorders, cancer
IL-1 alpha	GeneSeq Accession P90108	EP324447	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Matthews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Orencole & Dinarello (1989) <i>Cytokine</i> 1, 14-20.	inflammatory disorders, immunologic disorders, cancer

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
IL-3 variants	GeneSeq Accession R38561, R38562, R38563, R38564, R38565, R38566, R38567, R38568, R38569, R38570, R38571, and R38572	WO9307171	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Matthews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Aarden et al (1987) Eur. J. Immunol 17, 1411-16.	inflammatory disorders, immunologic disorders, cancer
IL-6	GeneSeq Accession R45717 and R45718	WO9402512	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Matthews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Aarden et al (1987) Eur. J. Immunol 17, 1411-16.	inflammatory disorders, immunologic disorders, cancer
IL-13	GeneSeq Accession R48624	WO9404680	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Matthews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Bouteiller et al (1995) J. Immunol. Methods 181, 29.	inflammatory disorders, immunologic disorders, cancer

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
IL-4 mutein Y124X	GeneSeq Accession R47182	DE4137333	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Matthews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Siegel & Mostowski (1990) <i>J Immunol Methods</i> 132,287-295.	inflammatory disorders, immunologic disorders, cancer
IL-4 mutein Y124G	GeneSeq Accession R47184	DE4137333	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Matthews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Siegel & Mostowski (1990) <i>J Immunol Methods</i> 132,287-295.	inflammatory disorders, immunologic disorders, cancer
Human Interleukin-10 (precursor)	GeneSeq Accession R41664	WO9317698	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Matthews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Thompson-Snipes et al (1991) <i>J. Exp. Med.</i> 173, 507-510.	inflammatory disorders, immunologic disorders, cancer

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
Human Interleukin-10	GeneSeq Accession R42642	WO9318783-A	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Matthews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Thompson-Snipes et al (1991) <i>J. Exp. Med.</i> 173, 507-510.	inflammatory disorders, immunologic disorders, cancer
Human interleukin-1 beta precursor.	GeneSeq Accession R42447	EP569042	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Matthews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Orencole & Dinarello (1989) <i>Cytokine</i> 1, 14-20.	inflammatory disorders, immunologic disorders, cancer
Interleukin-1alpha	GeneSeq Accession R45364	EP578278	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Matthews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225.	inflammatory disorders, immunologic disorders, cancer
Human interleukin-3 variant	GeneSeq Accession R22814	JP04063595	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Matthews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Kitamura et al (1989) <i>J Cell Physiol.</i> 140 323-334.	inflammatory disorders, immunologic disorders, cancer



Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
IL-1 $\beta$ fragments	GeneSeq Accession R35484 and R35485	EP541920	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Matthews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Orencole & Dinarello (1989) Cytokine 1, 14-20.	inflammatory disorders, immunologic disorders, cancer
IL-1 inhibitor (IL-1 $\beta$ )	GeneSeq Accession R35486 and R35484	EP541920	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Matthews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Orencole & Dinarello (1989) Cytokine 1, 14-20.	inflammatory disorders, immunologic disorders, cancer
ICE 22kD subunit.	GeneSeq Accession R33780	EP533350	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Matthews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225.	inflammatory disorders, immunologic disorders, cancer
ICE 20kD subunit.	GeneSeq Accession R33781	EP533350	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Matthews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225.	inflammatory disorders, immunologic disorders, cancer

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
ICE 10kD subunit	GeneSeq Accession R33782	EP533350	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Matthews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225.	inflammatory disorders, immunologic disorders, cancer
Human Interleukin-10 (precursor)	GeneSeq Accession R41664	WO9317698	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Matthews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Thompson-Snipes et al (1991) J. Exp. Med. 173, 507-510.	inflammatory disorders, immunologic disorders, cancer
Human Interleukin-10	GeneSeq Accession R42642	WO9318783	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Matthews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Thompson-Snipes et al (1991) J. Exp. Med. 173, 507-510.	inflammatory disorders, immunologic disorders, cancer
Human Interleukin-1 beta precursor	GeneSeq Accession R42447	EP569042	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Matthews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Kitamura et al (1989) J Cell Physiol. 140 323-334.	inflammatory disorders, immunologic disorders, cancer

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
Human interleukin-6	GeneSeq Accession R49041	WO9403492	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Matthews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Aarden et al (1987) Eur. J. Immunol 17, 1411-16.	inflammatory disorders, immunologic disorders, cancer
Mutant Interleukin 6 S176R	GeneSeq Accession R54990	WO9411402	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Matthews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Aarden et al (1987) Eur. J. Immunol 17, 1411-16.	inflammatory disorders, immunologic disorders, cancer
Interleukin 6	GeneSeq Accession R55256	JP06145063	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Matthews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Aarden et al (1987) Eur. J. Immunol 17, 1411-16.	inflammatory disorders, immunologic disorders, cancer
Interleukin 8 (IL-8) receptor	GeneSeq Accession R53932	JP06100595	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Matthews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Holmes et al (1991) Science 253, 1278-80.	Soluble IL-8 receptor polypeptides may be useful for inhibiting interleukin activities.

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
Human interleukin-7	GeneSeq Accession R59919	US5328988	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Matthews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Park et al (1990) J. Exp. Med. 171, 1073-79.	inflammatory disorders, immunologic disorders, cancer
IL-3 containing fusion protein.	GeneSeq Accession R79342 and R79344	WO9521254	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Matthews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Kitamura et al (1989) J Cell Physiol. 140 323-334.	inflammatory disorders, immunologic disorders, cancer

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
IL-3 mutant proteins	GeneSeq Accession R79254, R79255, R79256, R79257, R79258, R79259, R79260, R79261, R79262, R79263, R79264, R79265, R79266, R79267, R79268, R79269, R79270, R79271, R79272, R79273, R79274, R79275, R79276, R79277, R79278, R79279, R79280, R79281, R79282, R79283, R79284, and R79285	ZA9402636	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Matthews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Giri et al (1994) EMBO J. 13 2822-2830.	inflammatory disorders, immunologic disorders, cancer

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
IL-12 p40 subunit.	GeneSeq Accession R63018	AU9466072	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Matthews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225.	inflammatory disorders, immunologic disorders, cancer
AGF	GeneSeq Accession R64240	WO9429344	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Matthews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225.	inflammatory disorders, immunologic disorders, cancer
Human interleukin-12 40 kD subunit	GeneSeq Accession R79187	WO9519786	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Matthews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Hori et al (1987), Blood 70, 1069-1078.	inflammatory disorders, immunologic disorders, cancer
Human interleukin-15 receptor from clone P1	GeneSeq Accession R90843	WO9530695	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Matthews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Giri et al (1994) EMBO J. 13 2822-2830.	Soluble IL-8 receptor polypeptides may be useful for inhibiting interleukin activities.

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
Human interleukin-7	GeneSeq Accession R92796	WO9604306	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Matthews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Park et al (1990) J. Exp. Med. 171, 1073-79.	inflammatory disorders, immunologic disorders, cancer
interleukin-9	GeneSeq Accession R92797	WO9604306	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Matthews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Yang et al (1989) Blood 74, 1880-84.	inflammatory disorders, immunologic disorders, cancer
interleukin-3	GeneSeq Accession R92801	WO9604306	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Matthews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Kitamura et al (1989) J Cell Physiol. 140 323-334.	inflammatory disorders, immunologic disorders, cancer
Human interleukin-5	GeneSeq Accession R92802	WO9604306	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Matthews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Kitamura et al (1989) J Cell Physiol. 140 323-334.	inflammatory disorders, immunologic disorders, cancer

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
Recombinant interleukin-16	GeneSeq Accession W33373	DE19617202	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Matthews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Lim et al (1996) <i>J. Immunol.</i> 156, 2566-70.	inflammatory disorders, immunologic disorders, cancer
Human IL-16 protein	GeneSeq Accession W33234	DE19617202	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Matthews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Lim et al (1996) <i>J. Immunol.</i> 156, 2566-70.	inflammatory disorders, immunologic disorders, cancer
Thrl 17 human interleukin 9	GeneSeq Accession W27521	WO9708321	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Matthews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225.	inflammatory disorders, immunologic disorders, cancer
Metl 17 human interleukin 9	GeneSeq Accession W27522	WO9708321	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Matthews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Yang et al (1989) <i>Blood</i> 74, 1880-84.	inflammatory disorders, immunologic disorders, cancer



Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
Human intracellular IL-1 receptor antagonist.	GeneSeq Accession W77158	EP864585	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Matthews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Orencole & Dinarello (1989) Cytokine 1, 14-20.	inflammatory disorders, immunologic disorders, cancer
Human interleukin-18 protein (IL-18)	GeneSeq Accession W77158	EP864585	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Matthews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and USHIO et al (1996) J. Immunol. 156, 4274-79.	inflammatory disorders, immunologic disorders, cancer
Human interleukin-18	GeneSeq Accession W77077	EP861663	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Matthews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and USHIO et al (1996) J. Immunol. 156, 4274-79.	inflammatory disorders, immunologic disorders, cancer
Human interleukin 18 derivatives	GeneSeq Accessions W77083, W77084, W77085, W77086, W77087, W77088, and W77089	EP861663	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Matthews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Ushio et al (1996) J. Immunol. 156, 4274-79.	inflammatory disorders, immunologic disorders, cancer

Therapeutic Protein X	Exemplary Identifier	PC/T/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
Interleukin-9 (IL-9) mature protein variant (Met117 version).	GeneSeq Accession W68158	WO9827997	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Matthews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Yang et al (1989) Blood 74, 1880-84.	inflammatory disorders, immunologic disorders, cancer
IL-9 mature protein variant (Met117 version)	GeneSeq Accession W68157	WO9827997	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Matthews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Yang et al (1989) Blood 74, 1880-84.	inflammatory disorders, immunologic disorders, cancer
Human IL-9 receptor protein variant #3.	GeneSeq Accession W64058	WO9824904	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Matthews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Yang et al (1989) Blood 74, 1880-84.	inflammatory disorders, immunologic disorders, cancer
Human IL-9 receptor protein variant fragment	GeneSeq Accession W64060	WO9824904	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Matthews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Yang et al (1989) Blood 74, 1880-84.	Soluble IL-9 receptor polypeptides may be useful for inhibiting interleukin activities.

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
Human IL-9 receptor protein variant #3.	GeneSeq Accession W64061	WO9824904	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Matthews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Yang et al (1989) Blood 74, 1880-84.	Soluble IL-9 receptor polypeptides may be useful for inhibiting interleukin activities.
Human Interleukin-12 p40 protein	GeneSeq Accession W51311	WO9817689	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Matthews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Hori et al (1987), Blood 70, 1069-1078.	inflammatory disorders, immunologic disorders, cancer
Human Interleukin-12 p35 protein	GeneSeq Accession W51312	WO9817689	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Matthews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Hori et al (1987), Blood 70, 1069-1078.	inflammatory disorders, immunologic disorders, cancer
Human protein with IL-16 activity	GeneSeq Accession W63753	DE19649233-	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Matthews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Lim et al (1996) J. Immunol. 156, 2566-70.	inflammatory disorders, immunologic disorders, cancer

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
Human protein with IL-16 activity	GeneSeq Accession W59425	DE19649233-	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Matthews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Lim et al (1996) <i>J. Immunol.</i> 156, 2566-70.	inflammatory disorders, immunologic disorders, cancer
Human interleukin-15	GeneSeq Accession W53878	US5747024	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Matthews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Giri et al (1994) <i>EMBO J.</i> 13 2822-2830.	inflammatory disorders, immunologic disorders, cancer
Human wild-type interleukin-4 (hIL-4) protein	GeneSeq Accession W52149	WO9747744	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Matthews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Siegel & Mostowski (1990) <i>J Immunol Methods</i> 132,287-295.	inflammatory disorders, immunologic disorders, cancer

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
interleukin-4 muteins	GeneSeq Accessions W52150, W52151, W52153, W52154, W52155, W52156, W52157, W52158, W52159, W52160, W52161, W52162, W52163, W52164, W52165, W52166, and W52167	WO9747744	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Mathews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Siegel & Mostowski (1990) <i>J Immunol Methods</i> 132,287-295.	inflammatory disorders, immunologic disorders, cancer
Human interleukin 1 delta	GeneSeq Accession Y28408	WO9935268	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Mathews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Orencole & Dinarello (1989) <i>Cytokine</i> 1, 14-20.	inflammatory disorders, immunologic disorders, cancer
Human interleukin-1 receptor antagonist beta	GeneSeq Accession Y24395	WO9935268	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Mathews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Orencole & Dinarello (1989) <i>Cytokine</i> 1, 14-20.	inflammatory disorders, immunologic disorders, cancer

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
Human EDIRF II protein sequence	GeneSeq Accession Y22199	WO9932632	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Mathews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225.	inflammatory disorders, immunologic disorders, cancer
Human EDIRF I protein sequence	GeneSeq Accession Y22197	WO9932632	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Mathews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225.	inflammatory disorders, immunologic disorders, cancer
Human IL-1RD10 protein sequence	GeneSeq Accession Y14131	WO9919480	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Mathews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Orencole & Dinarello (1989) Cytokine 1, 14-20.	Soluble IL-1RD10 receptor polypeptides may be useful for inhibiting interleukin activities.
Human IL-1RD9	GeneSeq Accession Y14122	WO9919480	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Mathews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Orencole & Dinarello (1989) Cytokine 1, 14-20.	Soluble IL-1RD10 receptor polypeptides may be useful for inhibiting interleukin activities.

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
Human DNAX interleukin-40	GeneSeq Accession Y09196	WO9919491	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Matthews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225.	inflammatory disorders, immunologic disorders, cancer
(DIL-40) alternative sequence	GeneSeq Accession Y09197	WO9919491	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Matthews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225.	inflammatory disorders, immunologic disorders, cancer
IL-11	GeneSeq Accession R50176	WO9405318	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Matthews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Lu et al (1994) J Immunol. Methods 173, 19.	inflammatory disorders, immunologic disorders, cancer
Human adipogenesis inhibitory factor	GeneSeq Accession R43260	EP566410	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Matthews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225.	inflammatory disorders, immunologic disorders, cancer

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
IL-11	GeneSeq Accession W02202	JP08127539	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Mathews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Lu et al (1994) J Immunol. Methods 173, 19.	inflammatory disorders, immunologic disorders, cancer
IL-14	GeneSeq Accession R55800	WO9416074	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Mathews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Ambrus et al (1993) PNAS 90, 63330-34.	inflammatory disorders, immunologic disorders, cancer
IL-17 receptor	GeneSeq Accession B03807	US6072033	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Mathews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Yao et al (1995) J. Immunol. 155, 5483-86.	Soluble IL-17 receptor polypeptides may be useful for inhibiting interleukin activities.
IL-17	GeneSeq Accession R76573	WO9518826	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Mathews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Yao et al (1995) J. Immunol. 155, 5483-86.	inflammatory disorders, immunologic disorders, cancer



Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
CTLA-8	GeneSeq Accession W13651	WO9704097	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Mathews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225.	inflammatory disorders, immunologic disorders, cancer
IL-19	GeneSeq Accession W37935	WO9808870	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Mathews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Gallagher et al (2000) <i>Genes Immun.</i> 1, 442-50.	inflammatory disorders, immunologic disorders, cancer
IL-21 (TIF)	GeneSeq Accession Y92879	WO0024758	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Mathews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Parrish-Novak et al (2000) <i>Nature</i> 408, 57-63.	inflammatory disorders, immunologic disorders, cancer
IL-8 receptor	GeneSeq Accession R33420	WO9306229	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Mathews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Holmes et al (1991) <i>Science</i> 253, 1278-80.	Soluble IL-8 receptor polypeptides may be useful for inhibiting interleukin activities.

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
Human type II interleukin-1 receptor	GeneSeq Accession R85480	US5464937	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Matthews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Orencole & DiNarello (1989) Cytokine 1, 14-20.	Soluble type II interleukin-1 receptor polypeptides may be useful for inhibiting interleukin activities.
Human interleukin-12 receptor	GeneSeq Accession R69632	EP638644	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Matthews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Hori et al (1987), Blood 70, 1069-1078.	Soluble IL-12 receptor polypeptides may be useful for inhibiting interleukin activities.
Interleukin 8 receptor B	GeneSeq Accession R80758	US5440021	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Matthews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Holmes et al (1991) Science 253, 1278-80.	Soluble IL-8 receptor B polypeptides may be useful for inhibiting interleukin activities.
Human IL-8 receptor protein hIL8RA	GeneSeq Accession B09989	JP08103276	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Matthews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Holmes et al (1991) Science 253, 1278-80.	Soluble IL-8 receptor A polypeptides may be useful for inhibiting interleukin activities.

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
Human IL-8 receptor protein hIL8R	GeneSeq Accession B09990	JP08103276	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Mathews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Holmes et al (1991) Science 253, 1278-80.	Soluble IL-8 receptor polypeptides may be useful for inhibiting interleukin activities.
Interleukin-2 receptor associated protein p43	GeneSeq Accession R97569	WO9621732-	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Mathews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Gillis et al (1978) J. Immunol. 120, 2027.	Soluble IL-2 receptor polypeptides may be useful for inhibiting interleukin activities.
Human interleukin-17 receptor	GeneSeq Accession W04185	WO9629408	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Mathews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Yao et al (1995) J. Immunol. 155, 5483-86.	Soluble IL-17 receptor polypeptides may be useful for inhibiting interleukin activities.
Human interleukin-11 receptor	GeneSeq Accession R99090	WO9619574	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Mathews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Lu et al (1994) J. Immunol. Methods 173, 19.	Soluble IL-11 receptor polypeptides may be useful for inhibiting interleukin activities.

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
Human interleukin-1 receptor accessory protein	GeneSeq Accession W01911	WO9623067	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Mathews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Orencole & Dinarello (1989) Cytokine 1, 14-20.	Inflammatory disorders, immunologic disorders, cancer
AGF Protein	GeneSeq Accession R92749	US5488032	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Mathews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225.	Inflammatory disorders, immunologic disorders, cancer
Human interleukin-1 type-3 receptor	GeneSeq Accession R91064	W09607739	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Mathews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Orencole & Dinarello (1989) Cytokine 1, 14-20.	Soluble IL-type-3 receptor polypeptides may be useful for inhibiting interleukin activities
Human interleukin-13 beta receptor	GeneSeq Accession W24972	WO9720926	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Mathews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Boulter et al (1995) J. Immunol. Methods 181, 29.	Soluble IL-13 beta receptor polypeptides may be useful for inhibiting interleukin activities.

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
Human interleukin-13 alpha receptor	GeneSeq Accession W24973	WO9720926	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Matthews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Boutellier et al (1995) <i>J. Immunol. Methods</i> 181, 29.	Soluble IL-13 alpha receptor polypeptides may be useful for inhibiting interleukin activities.
Human interleukin-4 receptor	GeneSeq Accession W13499	US5599905	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Matthews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Siegel & Mostowski (1990) <i>J Immunol Methods</i> 132, 287-295.	Soluble IL-4 receptor polypeptides may be useful for inhibiting interleukin activities.
Human interleukin-12 beta-2 receptor	GeneSeq Accession W12771	EP759466	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Matthews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Hori et al (1987), <i>Blood</i> 70, 1069-1078.	Soluble IL-12 beta-2 receptor polypeptides may be useful for inhibiting interleukin activities.
Human interleukin-12 beta-1 receptor.	GeneSeq Accession W12772	EP759466	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Matthews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Hori et al (1987), <i>Blood</i> 70, 1069-1078.	Soluble IL-12 beta-1 receptor polypeptides may be useful for inhibiting interleukin activities.

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
Human IL-9 receptor protein	GeneSeq Accessions W64055, W64056, and W64057	WO9824904	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Mathews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Yang et al (1989), Blood 74, 1880-84..	Soluble IL-9 receptor polypeptides may be useful for inhibiting interleukin activities.
IL-10 receptor	GeneSeq Accession W41804	US5716804	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Mathews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Thompson-Snipes et al (1991) J. Exp. Med. 173, 507-510.	Soluble IL-10 receptor polypeptides may be useful for inhibiting interleukin activities.
Human IL-6 receptor	GeneSeq Accession Y30938	JP11196867	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Mathews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Aarden et al (1987) Eur. J. Immunol 17, 1411-16.	Soluble IL-6 receptor polypeptides may be useful for inhibiting interleukin activities.
IL-17 receptor	GeneSeq Accession Y97181	US6096305	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Mathews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Yao et al (1995) J. Immunol. 155, 5483-86.	Soluble IL-17 receptor polypeptides may be useful for inhibiting interleukin activities.

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
IL-17 receptor	GeneSeq Accession Y97131	US6100235	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Mathews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Yao et al (1995) J. Immunol. 155, 5483-86.	Soluble IL-17 receptor polypeptides may be useful for inhibiting interleukin activities.
Human interleukin-3 receptor	GeneSeq Accession R25300	EP509826	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Mathews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Kitamura et al (1989) J Cell Physiol. 140 323-334.	Soluble IL-3 receptor polypeptides may be useful for inhibiting interleukin activities.
Human GM-CSF receptor	GeneSeq Accession R10919	WO9102063	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Mathews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225.	Soluble GM-CSF receptor polypeptides may be useful for inhibiting interleukin activities.
Human IL-5 receptor alpha chain	GeneSeq Accession R25064	EP492214	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Mathews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Kitamura et al (1989) J Cell Physiol. 140, 323-334.	Soluble IL-5 receptor alpha polypeptides may be useful for inhibiting interleukin activities.

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
IL-5 receptor	GeneSeq Accession W82842	WO9847923	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Mathews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Kitamura et al (1989) J Cell Physiol. 140, 323-334.	Soluble IL-5 receptor polypeptides may be useful for inhibiting interleukin activities.
IL-6 receptor	GeneSeq Accession R37215	JP05091892	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Mathews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Aarden et al (1987) Eur. J. Immunol 17, 1411-16.	Soluble IL-6 receptor polypeptides may be useful for inhibiting interleukin activities.
Human B cell stimulating factor-2 receptor	GeneSeq Accession P90525	AU8928720	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Mathews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225.	Soluble B cell stimulating factor-2 receptor polypeptides may be useful for inhibiting interleukin activities.
IL-7 receptor clone	GeneSeq Accession R08330	EP403114	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Mathews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Park et al (1990) J. Exp. Med. 171, 1073-79.	Soluble IL-7 receptor polypeptides may be useful for inhibiting interleukin activities.



Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
EPO receptor; EPOR	GeneSeq Accession R06512	WO9008822	EPO Receptor is involved in the proliferation and differentiation of erythroblasts.	EPO Receptor activity can be determined using assays known in the art, such as, J Biol Chem 2001 Mar 23;276(12:8995-9002; JAK2 protein tyrosine kinase activity: Blood 1994 Sep 1;84(5):1501-7 and Mol Cell Biol. 1994 Oct;14(10):6506-14.	Inflammatory disorders, immunologic disorders, cancer, erythroblast proliferation and differentiation
IL-15 receptor	GeneSeq Accession R90843	WO9530695	Interleukins are a group of multifunctional cytokines synthesized by lymphocytes, monocytes, and macrophages. Known functions include stimulating proliferation of immune cells (e.g., T helper cells, B cells, eosinophils, and lymphocytes), chemotaxis of neutrophils and T lymphocytes, and/or inhibition of interferons.	Interleukin activity can be determined using assays known in the art: Matthews et al., in <i>Lymphokines and Interferons: A Practical Approach</i> , Clemens et al., eds, IRL Press, Washington, D.C. 1987, pp. 221-225; and Gini et al (1994) EMBO J. 13 2822-2830.	Soluble IL-15 receptor polypeptides may be useful for inhibiting interleukin activities.
CD137/4-1BB Receptor Protein	GeneSeq Accession R70977	WO9507984	Activities associated with apoptosis, NF-kB activation, and co-stimulation of immune cells such as T and B cells.	Apoptosis activity, NF-kB activation, and B and T cell co-stimulation can be determined using assays known in the art: Moore et al., 1999, Science, 285(5425):260-3; Song HY et al., 1997 Proc Natl Acad Sci U S A 94(18):9792-6; Epsevik and Nissen-Meyer, 1986, J. Immunol. Methods.	Soluble 4-1BB receptor polypeptides may be useful for inhibiting apoptosis, NF-kB activation, and/or co-stimulation of immune cells such as B and T cells.
BCMA	GeneSeq Accession Y71979	WO0068378	Activities associated with apoptosis, NF-kB activation, and co-stimulation of immune cells such as T and B cells.	Apoptosis activity, NF-kB activation, and B and T cell co-stimulation can be determined using assays known in the art: Moore et al., 1999, Science, 285(5425):260-3; Song HY et al., 1997 Proc Natl Acad Sci U S A 94(18):9792-6; Epsevik and Nissen-Meyer, 1986, J. Immunol. Methods.	Soluble BCMA receptor polypeptides may be useful for inhibiting apoptosis, NF-kB activation, and/or co-stimulation of immune cells such as B and T cells.

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
CD27	GeneSeq Accession R20814	WO9201049	Activities associated with apoptosis, NF-kB activation, and co-stimulation of immune cells such as T and B cells.	Apoptosis activity, NF-kB activation, and B and T cell co-stimulation can be determined using assays known in the art: Moore et al., 1999, Science, 285(5425):260-3; Song HY et al., 1997 Proc Natl Acad Sci U S A 94(18):9792-6; Epsevik and Nissen-Meyer, 1986, J. Immunol. Methods.	Soluble CD27 polypeptides may be useful for inhibiting apoptosis, NF-kB activation, and/or co-stimulation of immune cells such as B and T cells.
CD30	GeneSeq Accession R35478	DE4200043	Activities associated with apoptosis, NF-kB activation, and co-stimulation of immune cells such as T and B cells.	Apoptosis activity, NF-kB activation, and B and T cell co-stimulation can be determined using assays known in the art: Moore et al., 1999, Science, 285(5425):260-3; Song HY et al., 1997 Proc Natl Acad Sci U S A 94(18):9792-6; Epsevik and Nissen-Meyer, 1986, J. Immunol. Methods.	Soluble CD30 polypeptides may be useful for inhibiting apoptosis, NF-kB activation, and/or co-stimulation of immune cells such as B and T cells.
CD40	GeneSeq Accession Y33499	WO9945944	Activities associated with apoptosis, NF-kB activation, and co-stimulation of immune cells such as T and B cells.	Apoptosis activity, NF-kB activation, and B and T cell co-stimulation can be determined using assays known in the art: Moore et al., 1999, Science 285(5425):260-3; Song HY et al., 1997 Proc Natl Acad Sci U S A 94(18):9792-6; Epsevik and Nissen-Meyer, 1986, J. Immunol. Methods.	Soluble CD40 polypeptides may be useful for inhibiting apoptosis, NF-kB activation, and/or co-stimulation of immune cells such as B and T cells.

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
EDAR	Genbank Accession AAD50077		Activities associated with apoptosis, NF-kB activation, and co-stimulation of immune cells such as T and B cells.	Apoptosis activity, NF-kB activation, and B and T cell co-stimulation can be determined using assays known in the art: Moore et al., 1999, Science, 285(5425):260-3; Song HY et al., 1997 Proc Natl Acad Sci U S A 94(18):9792-6; Epsevik and Nissen-Meyer, 1986, J. Immunol. Methods.	Immune Disorders, Lymphomas, X-linked hypohidrotic ectodermal dysplasia
OX40; ACT-4	GeneSeq Accession R74737	WO9512673	Activities associated with apoptosis, NF-kB activation, and co-stimulation of immune cells such as T and B cells.	Apoptosis activity, NF-kB activation, and B and T cell co-stimulation can be determined using assays known in the art: Moore et al., 1999, Science, 285(5425):260-3; Song HY et al., 1997 Proc Natl Acad Sci U S A 94(18):9792-6; Epsevik and Nissen-Meyer, 1986, J. Immunol. Methods.	Immune Disorders, Lymphomas, T cell disorders
TACI	GeneSeq Accession W75783	WO9839361	Activities associated with apoptosis, NF-kB activation, and co-stimulation of immune cells such as T and B cells.	Apoptosis activity, NF-kB activation, and B and T cell co-stimulation can be determined using assays known in the art: Moore et al., 1999, Science, 285(5425):260-3; Song HY et al., 1997 Proc Natl Acad Sci U S A 94(18):9792-6; Epsevik and Nissen-Meyer, 1986, J. Immunol. Methods.	Soluble TACI receptor polypeptides may be useful for inhibiting apoptosis, NF-kB activation, and/or co-stimulation of immune cells such as B and T cells.
TNF-R	GeneSeq Accession R10986	AU9058976	Activities associated with apoptosis, NF-kB activation, and co-stimulation of immune cells such as T and B cells.	Apoptosis activity, NF-kB activation, and B and T cell co-stimulation can be determined using assays known in the art: Moore et al., 1999, Science, 285(5425):260-3; Song HY et al., 1997 Proc Natl Acad Sci U S A 94(18):9792-6; Epsevik and Nissen-Meyer, 1986, J. Immunol. Methods.	Soluble TNF-R receptor polypeptides may be useful for inhibiting apoptosis, NF-kB activation, and/or co-stimulation of immune cells such as B and T cells.

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
TNF-RII; TNF p75 receptor; Death Receptor	GeneSeq Accession R11141	EP418014	Activities associated with apoptosis, NF-kB activation, and co-stimulation of immune cells such as T and B cells.	Apoptosis activity, NF-kB activation, and B and T cell co-stimulation can be determined using assays known in the art: Moore et al., 1999, Science, 285(5425):260-3; Song HY et al., 1997 Proc Natl Acad Sci U S A 94(18):9792-6; Epsevik and Nissen-Meyer, 1986, J. Immunol. Methods.	Soluble TNFR-II receptor polypeptides may be useful for inhibiting apoptosis, NF-kB activation, and/or co-stimulation of immune cells such as B and T cells.
hAPO-4; TROY	GeneSeq Accession W93581	WO9911791	Activities associated with apoptosis, NF-kB activation, and co-stimulation of immune cells such as T and B cells.	Apoptosis activity, NF-kB activation, and B and T cell co-stimulation can be determined using assays known in the art: Moore et al., 1999, Science, 285(5425):260-3; Song HY et al., 1997 Proc Natl Acad Sci U S A 94(18):9792-6; Epsevik and Nissen-Meyer, 1986, J. Immunol. Methods.	Immune Disorders, Cancers
TNF-alpha precursor	GeneSeq Accession P60074	EP205038	Activities associated with apoptosis, NF-kB activation, and co-stimulation of immune cells such as T and B cells.	Apoptosis activity, NF-kB activation, and B and T cell co-stimulation can be determined using assays known in the art: Moore et al., 1999, Science, 285(5425):260-3; Song HY et al., 1997 Proc Natl Acad Sci U S A 94(18):9792-6; Epsevik and Nissen-Meyer, 1986, J. Immunol. Methods.	Inflammatory disorders, immunologic disorders, cancer
Human TNF-alpha	GeneSeq Accession R62463	EP619372	Activities associated with apoptosis, NF-kB activation, and co-stimulation of immune cells such as T and B cells	Apoptosis activity, NF-kB activation, and B and T cell co-stimulation can be determined using assays known in the art: Moore et al., 1999, Science, 285(5425):260-3; Song HY et al., 1997 Proc Natl Acad Sci U S A 94(18):9792-6; Epsevik and Nissen-Meyer, 1986, J. Immunol. Methods.	Inflammatory disorders, immunologic disorders, cancer

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
Human TNF-alpha	GeneSeq Accession R42679	EP563714	Activities associated with apoptosis, NF-kB activation, and co-stimulation of immune cells such as T and B cells.	Apoptosis activity, NF-kB activation, and B and T cell co-stimulation can be determined using assays known in the art: Moore et al., 1999, Science, 285(5425):260-3; Song HY et al., 1997 Proc Natl Acad Sci U S A 94(18):9792-6; Epsevik and Nissen-Meyer, 1986, J. Immunol. Methods.	Inflammatory disorders, immunologic disorders, cancer
Human TNF-beta (LT-alpha)	GeneSeq Accession B37799	WO0064479	Activities associated with apoptosis, NF-kB activation, and co-stimulation of immune cells such as T and B cells.	Apoptosis activity, NF-kB activation, and B and T cell co-stimulation can be determined using assays known in the art: Moore et al., 1999, Science, 285(5425):260-3; Song HY et al., 1997 Proc Natl Acad Sci U S A 94(18):9792-6; Epsevik and Nissen-Meyer, 1986, J. Immunol. Methods.	Inflammatory disorders, immunologic disorders, cancer
LT-alpha	GeneSeq Accession P70107	EP250000	Activities associated with apoptosis, NF-kB activation, and co-stimulation of immune cells such as T and B cells.	Apoptosis activity, NF-kB activation, and B and T cell co-stimulation can be determined using assays known in the art: Moore et al., 1999, Science, 285(5425):260-3; Song HY et al., 1997 Proc Natl Acad Sci U S A 94(18):9792-6; Epsevik and Nissen-Meyer, 1986, J. Immunol. Methods.	Inflammatory disorders, immunologic disorders, cancer
LT-beta	GeneSeq Accession R56869	WO9413808	Activities associated with apoptosis, NF-kB activation, and co-stimulation of immune cells such as T and B cells.	Apoptosis activity, NF-kB activation, and B and T cell co-stimulation can be determined using assays known in the art: Moore et al., 1999, Science, 285(5425):260-3; Song HY et al., 1997 Proc Natl Acad Sci U S A 94(18):9792-6; Epsevik and Nissen-Meyer, 1986, J. Immunol. Methods.	Inflammatory disorders, immunologic disorders, cancer

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
OPGL	GeneSeq Accession W83195	WO9846751	Activities associated with apoptosis, NF-kB activation, and co-stimulation of immune cells such as T and B cells.	Apoptosis activity, NF-kB activation, and B and T cell co-stimulation can be determined using assays known in the art: Moore et al., 1999, Science, 285(5425):260-3; Song HY et al., 1997 Proc Natl Acad Sci U S A 94(18):9792-6; Epsevik and Nissen-Meyer, 1986, J. Immunol. Methods.	Inflammatory disorders, immunologic disorders, cancer, loss of bone mass
FasL	GeneSeq Accession W98071	WO9903999	Activities associated with apoptosis, NF-kB activation, and co-stimulation of immune cells such as T and B cells.	Apoptosis activity, NF-kB activation, and B and T cell co-stimulation can be determined using assays known in the art: Moore, et al., 1999, Science, 285(5425):260-3; Song HY et al., 1997 Proc Natl Acad Sci U S A 94(18):9792-6; Epsevik and Nissen-Meyer, 1986, J. Immunol. Methods.	Inflammatory disorders, immunologic disorders, cancer
FasL	GeneSeq Accession W95041	WO9903998	Activities associated with apoptosis, NF-kB activation, and co-stimulation of immune cells such as T and B cells.	Apoptosis activity, NF-kB activation, and B and T cell co-stimulation can be determined using assays known in the art: Moore et al., 1999, Science, 285(5425):260-3; Song HY et al., 1997 Proc Natl Acad Sci U S A 94(18):9792-6; Epsevik and Nissen-Meyer, 1986, J. Immunol. Methods.	Inflammatory disorders, immunologic disorders, cancer
CD27L	GeneSeq Accession R50121	WO9405691	Activities associated with apoptosis, NF-kB activation, and co-stimulation of immune cells such as T and B cells.	Apoptosis activity, NF-kB activation, and B and T cell co-stimulation can be determined using assays known in the art: Moore et al., 1999, Science, 285(5425):260-3; Song HY et al., 1997 Proc Natl Acad Sci U S A 94(18):9792-6; Epsevik and Nissen-Meyer, 1986, J. Immunol. Methods.	Inflammatory disorders, immunologic disorders, cancer

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
CD30 ligand	GeneSeq Accession R45007	WO9324135	Activities associated with apoptosis, NF-kB activation, and co-stimulation of immune cells such as T and B cells.	Apoptosis activity, NF-kB activation, and B and T cell co-stimulation can be determined using assays known in the art: Moore et al., 1999, Science, 285(5425):260-3; Song HY et al., 1997 Proc Natl Acad Sci U S A 94(18):9792-6; Epsevik and Nissen-Meyer, 1986, J. Immunol. Methods.	Inflammatory disorders, immunologic disorders, cancer
CD40L	GeneSeq Accession R85486	WO9529935	Activities associated with apoptosis, NF-kB activation, and co-stimulation of immune cells such as T and B cells.	Apoptosis activity, NF-kB activation, and B and T cell co-stimulation can be determined using assays known in the art: Moore, et al., 1999, Science, 285(5425):260-3; Song HY et al., 1997 Proc Natl Acad Sci U S A 94(18):9792-6; Epsevik and Nissen-Meyer, 1986, J. Immunol. Methods.	Inflammatory disorders, immunologic disorders, cancer
4-1BB ligand	GeneSeq Accession W26657	US5674704	Activities associated with apoptosis, NF-kB activation, and co-stimulation of immune cells such as T and B cells.	Apoptosis activity, NF-kB activation, and B and T cell co-stimulation can be determined using assays known in the art: Moore et al., 1999, Science, 285(5425):260-3; Song HY et al., 1997 Proc Natl Acad Sci U S A 94(18):9792-6; Epsevik and Nissen-Meyer, 1986, J. Immunol. Methods.	Inflammatory disorders, immunologic disorders, cancer
FAS Ligand Inhibitory Protein (DcR3)	GeneSeq Accession B19335	WO0058465	Activities associated with apoptosis, NF-kB activation, and co-stimulation of immune cells such as T and B cells.	Apoptosis activity, NF-kB activation, and B and T cell co-stimulation can be determined using assays known in the art: Moore et al., 1999, Science, 285(5425):260-3; Song HY et al., 1997 Proc Natl Acad Sci U S A 94(18):9792-6; Epsevik and Nissen-Meyer, 1986, J. Immunol. Methods.	Soluble DcR3 polypeptides may be useful for inhibiting apoptosis, NF-kB activation, and/or co-stimulation of immune cells such as B and T cells.

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
OX40L	GeneSeq Accession R79903	WO9521915	Activities associated with apoptosis, NF-kB activation, and co-stimulation of immune cells such as T and B cells.	Apoptosis activity, NF-kB activation, and B and T cell co-stimulation can be determined using assays known in the art: Moore et al., 1999, Science, 285(5425):260-3; Song HY et al., 1997 Proc Natl Acad Sci U S A 94(18):9792-6; Epsevik and Nissen-Meyer, 1986, J. Immunol. Methods.	Inflammatory disorders, immunologic disorders, cancer
Protease inhibitor peptides	GeneSeq Accessions R12435, R12436, R12437, R12438, R12439, R12440, and R1244	WO9106561	Peptides that inhibit the function/binding of HIV	HIV protease activities are known in the art: HIV protease assays: EP0387231. One can modify the assay to look for inhibition using any of the disclosed protease inhibitor polypeptides.	HIV, inflammatory disorders, immunologic disorders, cancer, viral infections
Retroviral protease inhibitors	GeneSeq Accessions R06660, R06661, R06662, R06663, R06664, R06665, R06666, R06667, R06668, R06669, R06670, R06671, R06672, R06673, R06674, R06675, and R06676	EP387231	Peptides that inhibit the function/binding of HIV	HIV protease activities are known in the art: HIV protease assays: EP0387231. One can modify the assay to look for inhibition using any of the disclosed protease inhibitor polypeptides.	HIV, inflammatory disorders, immunologic disorders, cancer, viral infections



Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
HIV protease inhibiting peptides	GeneSeq Accessions R59293, R59294, R59295, R59296, R59297, R59298, R59299, R592300, R59301, R59302, R59301, R59302, R59303, R59304, R59305, R59306, R59307, R59308, R59309, R59310, R59311, R59312, R59313, R59314, R59315, R59316, R59317 R59318, R59319, R59320, R59321, R59322, R59323, R59324, R59325, R59326, R59327, R59328, R59329, R59330, R59331, R59332, R59333, R59334, R59335, R59336, R59337, R59338, R59339, R59340, R59341, R59342, R59343, R59344, R59345, R59346, R59347, R59348, R59349, and R59350	WO9301828	Peptides that inhibit the function/binding of HIV	HIV protease activities are known in the art. HIV protease assays: EP0387231. One can modify the assay to look for inhibition using any of the disclosed protease inhibitor polypeptides.	HIV, inflammatory disorders, immunologic disorders, cancer, viral infections

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
HIV-1 protease inhibitors	GeneSeq Accessions R86326, R86327, R86328, R86329, R86330, R86331, R86332, R86333, R86334, R86335, R86336, R86337, R86338, R86339, R86340, R86341, R86342, R86343, R86344, R86345, R86346, R86347, R86348, R86349, R86350, R86351, R86352, R86353, R86354, R86355, R86356, R86357, R86358, R86359, R86360, R86361, R86362, R86363, R86364, R86365, R86366, R86367, R86368, R86369, R86370, and R86371	DE4412174	Peptides that inhibit the function/binding of HIV	HIV protease activities are known in the art: HIV protease assays: EP0387231. One can modify the assay to look for inhibition using any of the disclosed protease inhibitor polypeptides.	HIV, inflammatory disorders, immunologic disorders, cancer, viral infections
HIV Inhibitor Peptide	GeneSeq Accession Y89687	WO9959615	Peptides that inhibit the function/binding of HIV	HIV protease activities are known in the art: HIV protease assays: EP0387231. One can modify the assay to look for inhibition using any of the disclosed protease inhibitor polypeptides.	HIV, inflammatory disorders, immunologic disorders, cancer, viral infections
HIV Inhibitor Peptide	GeneSeq Accession Y31955	WO9948513	Peptides that inhibit the function/binding of HIV	HIV Protease activities are known in the art; HIV protease assays: EP0387231. One can modify the assay to look for inhibition using any of the disclosed protease inhibitor polypeptides.	HIV, inflammatory disorders, immunologic disorders, cancer, viral infections.

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
HIV Inhibitor Peptide	GeneSeq Accession Y89687	WO9959615	Peptides that inhibit the function/binding of HIV	HIV protease activities are known in the art: HIV protease assays: EP0387231. One can modify the assay to look for inhibition using any of the disclosed protease inhibitor polypeptides.	HIV, inflammatory disorders, immunologic disorders, cancer, viral infections
HIV Inhibitor Peptide	GeneSeq Accession Y31955	WO9948513	Peptides that inhibit the function/binding of HIV	HIV Protease activities are known in the art: HIV protease assays: EP0387231. One can modify the assay to look for inhibition using any of the disclosed protease inhibitor polypeptides.	HIV, inflammatory disorders, immunologic disorders, cancer, viral infections.
HIV Inhibitor Peptide	<a href="http://www.sciencexpress.org">www.sciencexpress.org</a> Published online 12 January 2001; 10.1126/scienc e.1057453		Peptides that inhibit the function/binding of HIV	HIV protease activities are known in the art: HIV protease assays: EP0387231. One can modify the assay to look for inhibition using any of the disclosed protease inhibitor polypeptides.	HIV, inflammatory disorders, immunologic disorders, cancer, viral infections
Human monocyte chemoattractant factor hMCP-3	GeneSeq Accession R73915	WO9509232	Chemokines are a family of small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~ 17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols, Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ	Immune disorders, particularly useful for treating bacterial and/or viral meningitis

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
Human monocyte chemoattractant factor hMCP-1	GeneSeq Accession R73914	WO9509232	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~ 17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ	Immune disorders, particularly useful for treating bacterial and/or viral meningitis
Human gro-beta chemokine	GeneSeq Accessions R66699 and W17671	WO9429341	Chemokines are a family of small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~ 17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ	Immune disorders, inflammatory disorders, blood-related disorders, stem cell transplantation, cancer

<b>Therapeutic Protein X</b>	<b>Exemplary Identifier</b>	<b>PCT/Patent Reference</b>	<b>Biological Activity</b>	<b>Exemplary Activity Assay</b>	<b>Preferred Indication Y</b>
Human gro-gamma chemokine	GeneSeq Accessions R66700 and W17672	WO9429341	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~ 17 receptors thus far identified	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ	Immune disorders, inflammatory disorders, blood-related disorders, stem cell transplantation, cancer
Human gro-alpha chemokine	GeneSeq Accessions R66698 and W18024	WO9429341	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~ 17 receptors thus far identified	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ	Immune disorders, inflammatory disorders, blood-related disorders, stem cell transplantation, cancer

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
Human eosinophil-expressed chemokine (EEC)	GeneSeq Accession W05186	WO9632481	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~ 17 receptors thus far identified	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ	Immune disorders, particularly treatment of eosinophilia, inflammation, allergies, asthma, leukaemia and lymphoma
Chemokine-like protein PF4-414 Full-Length and Mature	GeneSeq Accessions R92318 and R99809	WO9613587	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~ 17 receptors thus far identified	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ	Cancer and blood-related disorders, particularly myelosuppression

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
Chemokine-like protein IL-8M3	GeneSeq Accession R99812	WO9613587	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~ 17 receptors thus far identified	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ; and Holmes et al (1991) Science 253, 1278-80.	Cancer and blood-related disorders, particularly myelosuppression
Human interleukin-8 (IL-8)	GeneSeq Accession R99814	WO9613587	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~ 17 receptors thus far identified	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ; and Holmes et al (1991) Science 253, 1278-80.	Cancer and blood-related disorders, particularly myelosuppression

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
Chemokine-like protein IL-8M1 Full-Length and Mature	GeneSeq Accessions R99815 and R99803	WO9613587	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~ 17 receptors thus far identified	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ; and Holmes et al (1991) Science 253, 1278-80.	Cancer and blood-related disorders, particularly myelosuppression
Chemokine-like protein IL-8M8 Full-Length and Mature	GeneSeq Accessions R99816 and R99805	WO9613587	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~ 17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ; and Holmes et al (1991) Science 253, 1278-80.	Cancer and blood-related disorders, particularly myelosuppression.



Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
Chemokine-like protein IL - 8/M8 Full-Length and Mature	GeneSeq Accessions R99817 and R99806	WO9613587	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~ 17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot; T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ; and Holmes et al (1991) Science 253, 1278-80.	Cancer and blood-related disorders, particularly myelosuppression.
Chemokine-like protein IL - 8/M8 Full-Length and Mature	GeneSeq Accessions R99818 and R99804	WO9613587	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~ 17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot; T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ; and Holmes et al (1991) Science 253, 1278-80.	Cancer and blood-related disorders, particularly myelosuppression.

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
Chemokine-like protein IL - 8/M8 Full-Length and Mature	GeneSeq Accessions R99819 and R99807	WO9613587	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~ 17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot; T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ	Cancer and blood-related disorders, particularly myelosuppression.
Chemokine-like protein IL - 8/M8 Full-Length and Mature	GeneSeq Accessions R99822 and R9807	WO9613587	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~ 17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot; T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ	Cancer and blood-related disorders, particularly myelosuppression.

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
Human foetal spleen expressed chemokine, FSEC	GeneSeq Accession R98499	WO9622374	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~ 17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot; T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ	Immune disorders
Liver expressed chemokine-1 (LVEC-1)	GeneSeq Accession R95689	WO9616979	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~ 17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot; T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ	Inflammation of the liver

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
Liver expressed chemokine-2(L-VEC-2)	GeneSeq Accession R95690	WO9616979	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~ 17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot; T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ	Inflammation of the liver
Pituitary expressed chemokine (PGEC)	GeneSeq Accession R95691	WO9616979	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~ 17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot; T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ	Inflammation, particularly of the liver

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
Adenoid-expressed chemokine (ADEC)	GeneSeq Accession R97664	WO9617868	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot; T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ	Inflammation, angiogenesis, tumorigenesis, musculoskeletal disorders
Human chemokineCC-2	GeneSeq Accession W38170	WO9741230	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc. Totowa, NJ	Immune disorders, cell migration, proliferation, and differentiation disorders

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
Human chemokine HCC-1	GeneSeq Accession W38171	WO9741230	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~ 17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in molecular Biology 2000, vol. 138: Chemokine Protocols. Edited by A.E.I. Proudfoot, T.N.C. Wells and C.A. Power © Humana Press Inc., Totowa, NJ	Immune disorders, cell migration, proliferation, and differentiation disorders
Human chemokine CC-3	GeneSeq Accession W38172	WO9741230	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~ 17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in molecular Biology, 2000, vol. 138: Chemokine Protocols, Edited by A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power © Humana Press Inc., Totowa, NJ	Immune disorders, cell migration, proliferation and differentiation disorders

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
Novel betachemokine designated PTEC	GeneSeq Accession W27271	WO9739126	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~ 17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in molecular Biology, 2000, vol. 138: Chemokine Protocols, Edited by A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power © Humana Press Inc., Totowa, NJ	Immune disorders, vascular disorders, cancer
Human CX3C 111 amino acid chemokine	GeneSeq Accession W23344	WO9727299	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~ 17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in molecular Biology, 2000, vol. 138: Chemokine Protocols, Edited by A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power © Humana Press Inc., Totowa, NJ	Immune disorders, inflammatory diseases, abnormal proliferation, regeneration, degeneration, and atrophy

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
Human CCF18 chemokine	GeneSeq Accession W25942	WO9721812	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~ 17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in molecular Biology, 2000, vol. 138: Chemokine Protocols, Edited by A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power © Humana Press Inc., Totowa, NJ	Abnormal physiology and development disorders, can also be used as an anti-viral agent
Human beta-chemokine H1305 (MCP-2)	GeneSeq Accession W26655	WO9725427	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~ 17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in molecular Biology, 2000, vol. 138: Chemokine Protocols, Edited by A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power © Humana Press Inc., Totowa, NJ	Chemotaxis, blood-related disorders, viral infection, HIV, wound healing, cancer



Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
Human eosinocyte CC type chemokine eotaxin	GeneSeq Accession W14990	WO9712914	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~ 17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in molecular Biology, 2000, vol. 138: Chemokine Protocols, Edited by A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power © Humana Press Inc., Totowa, NJ	Inflammatory and immune disorders
Human thymus and activation regulated cytokine (TARC)	GeneSeq Accession W14018	WO9711969	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~ 17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in molecular Biology, 2000, vol. 138: Chemokine Protocols, Edited by A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power © Humana Press Inc., Totowa, NJ	Inflammatory and immune disorders

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
Human chemokine beta-8 short forms	GeneSeq Accession W16315	WO9712041	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols, Edited by A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power © Humana Press Inc., Totowa, NJ	Cancer, wound healing, immune disorders
Microphage derived chemokine, MDC	GeneSeq Accession W20058	WO9640923	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. ©Humana Press Inc., Totowa, NJ	Inflammatory diseases, wound healing, angiogenesis

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
Human chemokine ZSIG-35	GeneSeq Accession W30565	WO9844117	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. ©Humana Press Inc., Totowa, NJ	Inflammatory and immune diseases
Primate CC chemokine "TLINCK"	GeneSeq Accession W69990	WO98328658	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. ©Humana Press Inc., Totowa, NJ	Immune and inflammatory disorders, abnormal proliferation, regeneration, generation and atrophy disorders
Primate CXC chemokine "BICK"	GeneSeq Accession W69989	WO9832858	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. ©Humana Press Inc., Totowa, NJ	Immune and inflammatory disorders, abnormal proliferation, regeneration, generation and atrophy disorders

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
Human CC-type chemokine protein designated SLC (secondary lymphoid chemokine)	GeneSeq Accession W69163	WO9831809	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. ©Humana Press Inc., Totowa, NJ	Immune, inflammatory, and infectious disorders, cancer
Human CC chemokine ELC protein	GeneSeq Accession W62542	WO9826071	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ	Cancer and infectious diseases, particularly herpes virus

<b>Therapeutic Protein X</b>	<b>Exemplary Identifier</b>	<b>PCT/Patent Reference</b>	<b>Biological Activity</b>	<b>Exemplary Activity Assay</b>	<b>Preferred Indication Y</b>
Human DVic-1 C-C chemokine	GeneSeq Accession W60649	W09823750	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ	Abnormal proliferation, regeneration, and degeneration, and atrophy disorders, including cancer
Human C-C chemokine DGWCC	GeneSeq Accession W60650	W09823750	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ	Immune disorders, cell proliferation disorders, cancer

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
Human STCP-1	GeneSeq Accession W62783	WO9824907	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ	Immune disorders, particularly T cell related disorders, viral infection, and inflammation, especially joint
Exodua protein	GeneSeq Accession W61279	WO9821330	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ	Immune and inflammatory disorders, angiogenesis, cancer, and proliferation disorders, particularly myeloproliferative diseases

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Human Chr19Kine protein	GeneSeq Accession W50887	WO9814581	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols, Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ	Cancer and degenerative disorders
Human T cell mixed lymphocyte reaction expressed chemokine (TMEC)	GeneSeq Accession W58703	US5780268	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols, Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power © Humana Press Inc., Totowa, NJ	Immune, inflammatory, and infectious disorders, cancer

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
Human 6CKine protein	GeneSeq Accession W50885	W09814581	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods of Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power © Humana Press Inc., Totowa, NJ	Cancer and degenerative disorders
human liver and activation regulated chemokine (LARC)	GeneSeq Accession W57475	WO9817800	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods of Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power © Humana Press Inc., Totowa, NJ	Immune, inflammatory, and infectious disorders, cancer



Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
RANTES peptide	GeneSeq Accession W29538	WO9744462	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods of Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power © Humana Press Inc., Totowa, NJ	Infectious diseases, particularly HIV
RANTES 8-68	GeneSeq Accession W29529	WO9744462	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods of Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power © Humana Press Inc., Totowa, NJ	Infectious diseases, particularly HIV

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
RANTES 9-68	GeneSeq Accession W29528	WO9744462	Chemokines area family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods of Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power © Humana Press Inc., Totowa, NJ	Infectious diseases, particularly HIV
Human chemokine protein 331D5	GeneSeq Accession W59433	WO9811226	Chemokines area family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods of Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power © Humana Press Inc., Totowa, NJ	Abnormal proliferation, regeneration, degeneration or atrophy, including cancer

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Human chemokine protein 61164	GeneSeq Accession W59430	WO9811226	Chemokines area family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Mehtods of Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power © Humana Press Inc., Totowa, NJ	Abnormal proliferation, regeneration, degeneration or atrophy, including cancer
Chemokine MCP-4	GeneSeq Accession W56690	WO9809171	Chemokines area family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Mehtods of Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power © Humana Press Inc., Totowa, NJ	Immune, Inflammatory, and infectious diseases

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication
Human stromal cell-derived chemokine, SDF-1	GeneSeq Accession W50766	FR2751658	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~ 17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ	HIV infections
Thymus expressed chemokine (TECK)	GeneSeq Accession W44397	WO9801557	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~ 17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ	Immune and inflammatory disorders

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Human chemokine MIP-3alpha	GeneSeq Accession W44398	WO9801557	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~ 17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ	Immune and inflammatory disorders
Human chemokine MIP-3beta	GeneSeq Accession W44399	WO9801557	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~ 17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ	Immune and inflammatory disorders

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Human monocyte chemotactic protein (MCP) sequence	GeneSeq Accession W42072	WO9802459	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~ 17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ	Immune disorders, respiratory disorders, cancer
Macrophage-derived chemokine (MDC)	GeneSeq Accessions W40811 and Y24414	US5688927/ US5932703	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~ 17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ	Immune, and inflammatory disorders, cancer

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
Macrophage derived chemokine analogue MDC-eyfy	GeneSeq Accession Y24416	US5932703	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~ 17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ	Immune and inflammatory disorders
Macrophage derived chemokine analogue MDC (n+1)	GeneSeq Accession Y24413	US5932703	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~ 17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ	Immune and inflammatory disorders

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Macrophage derived chemokine analogue MDC-yl	GeneSeq Accession Y24415	US5932703	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~ 17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ	Immune and inflammatory disorders
Human type CC chemokine eotaxin 3 protein sequence	GeneSeq Accession Y43178	JP11243960	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~ 17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ	Allergic diseases and HIV infection



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Human MCP-3 and human Muc-1 core epitope (VNT) fusion protein	GeneSeq Accession Y29893	WO9946392	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~ 17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ	Cancer and immune disorders, particularly HIV infection
Human IP-10 and human Muc-1 core epitope (VNT) fusion protein	GeneSeq Accession Y29894	WO9946392	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~ 17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ	Cancer and immune disorders, particularly HIV infection

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
Human IP-10 and HIV-1 gp 120 hypervariable region fusion protein	GeneSeq Accession Y29897	W09946392	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to $\sim 17$ receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ	Cancer and immune disorders, particularly HIV infection
Human mammary associated chemokine (MACK) protein Full-Length and Mature	GeneSeq Accessions Y29092 and Y29093	WO9936540	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to $\sim 17$ receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ	Breast disease, including cancer

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Tim-1 protein	GeneSeq Accession Y28290	WO9933990	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~ 17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ	Inflammation due to stimuli such as heart attacks and stroke, infection, physical trauma, UV or ionizing radiation, burns, frostbite or corrosive chemicals
Human Lkn-1 Full-Length and Mature protein	GeneSeq Accessions Y17280, Y17274, Y17281, and Y17275	WO9928473 and WO9928472	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~ 17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ	HIV infection and cancer, particularly leukemia

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N-terminal modified chemokine met-hSDF-1 alpha	GeneSeq Accession Y05818	WO9920759	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~ 17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ	Inhibit or stimulate angiogenesis, inhibit the binding of HIV
N-terminal modified chemokine met-hSDF-1 beta	GeneSeq Accession Y05819	WO9920759	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~ 17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ	Inhibit or stimulate angiogenesis, inhibit the binding of HIV, antiinflammatory; immunosuppressant

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N-terminal modified chemokine GroHEK/hSDF-1 $\alpha$	GeneSeq Accession Y05820	WO9920759	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to $\sim 17$ receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ	Inhibit or stimulate angiogenesis, inhibit the binding of HIV, antiinflammatory; immunosuppressant
N-terminal modified chemokine GroHEK/hSDF-1 $\beta$	GeneSeq Accession Y05821	WO9920759	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to $\sim 17$ receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ	Inhibit or stimulate angiogenesis, inhibit the binding of HIV, antiinflammatory; immunosuppressant

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Chemokine Eotaxin	GeneSeq Accession Y14230	WO9912968	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~ 17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ	Increase or enhance an inflammatory response, an immune response or haematopoietic cell-associated activity; treat a vascular indication; Cancer, enhance wound healing, to prevent or treat asthma, organ transplant rejection, rheumatoid arthritis or allergy
Chemokine hMCP1a	GeneSeq Accession Y14225	WO9912968	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~ 17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ	Immune disorders, Vascular disorders, Wound healing, cancer, prevent organ transplant rejection, Increase or enhance an inflammatory response,

<b>Therapeutic Protein X</b>	<b>Exemplary Identifier</b>	<b>PCT/Patent Reference</b>	<b>Biological Activity</b>	<b>Exemplary Activity Assay</b>	<b>Preferred Indication Y</b>
Chemokine hMCP1b	GeneSeq Accession Y14226	WO9912968	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ	Immune disorders, Vascular disorders, Wound healing, cancer, prevent organ transplant rejection, Increase or enhance an inflammatory response,
Chemokine hSDF1b	GeneSeq Accession Y14228	WO9912968	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ	Immune disorders, Vascular disorders, Wound healing, cancer, prevent organ transplant rejection, Increase or enhance an inflammatory response,

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
Chemokine hIL-8	GeneSeq Accession Y14229	WO9912968	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~ 17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ; and Holmes et al (1991) Science 253, 1278-80.	Immune disorders, Vascular disorders, Wound healing, cancer, prevent organ transplant rejection, Increase or enhance an inflammatory response,
Chemokine hMCP1	GeneSeq Accession Y14222	WO9912968	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~ 17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ	Immune disorders, Vascular disorders, Wound healing, cancer, prevent organ transplant rejection, Increase or enhance an inflammatory response,



Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
Chemokine hMCP2	GeneSeq Accession Y14223	WO9912968	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~ 17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ	Immune disorders, Vascular disorders, Wound healing, cancer, prevent organ transplant rejection, Increase or enhance an inflammatory response,
Chemokine hMCP3	GeneSeq Accession Y14224	WO9912968	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~ 17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ	Immune disorders, Vascular disorders, Wound healing, cancer, prevent organ transplant rejection, Increase or enhance an inflammatory response,

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
C-C chemokine, MCP2	GeneSeq Accession Y05300	EP905240	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~ 17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ	Inflammatory, Immune and infectious diseases; pulmonary diseases and skin disorders; tumours, and angiogenesis-and haematopoiesis-related diseases
Wild type monocyte chemotactic protein 2	GeneSeq Accession Y07233	EP906954	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~ 17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ	Inflammatory, Immune and infectious diseases; pulmonary diseases and skin disorders; tumours, and angiogenesis-and haematopoiesis-related diseases

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
Truncated monocyte chemotactic protein 2 (6-76)	GeneSeq Accession Y07234	EP906954	Chemokines area family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~ 17 receptors thus far identified.	Chemokines activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power, Humana Press Inc., Totowa, NJ	Inflammatory, immune and infectious diseases; pulmonary diseases and skin disorders; tumours, and angiogenesis-and haematopoiesis-related diseases
Truncated RANTES protein (3-68)	GeneSeq Accessions Y07236 and Y07232	EP905241; EP906954	Chemokines area family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~ 17 receptors thus far identified.	Chemokines activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power, Humana Press Inc., Totowa, NJ	Inflammatory, immune and infectious diseases; pulmonary diseases and skin disorders; tumours, and angiogenesis-and haematopoiesis-related diseases

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
Wild type monocyte chemoattractant protein 2	GeneSeq Accession Y07237	EP905241	Chemokines area family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~ 17 receptors thus far identified.	Chemokines activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power, Humana Press Inc., Totowa, NJ	Inflammatory, immune and infectious diseases; pulmonary diseases and skin disorders; tumours, and angiogenesis-related diseases
Truncated monocyte chemoattractant protein 2 (6-76)	GeneSeq Accession Y07238	EP905241	Chemokines area family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~ 17 receptors thus far identified.	Chemokines activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power, Humana Press Inc., Totowa, NJ	Inflammatory, immune and infectious diseases; pulmonary diseases and skin disorders; tumours, and angiogenesis-related diseases

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
A partial CXCR4B protein	GeneSeq Accession W97363	EP897980	Chemokines area family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~ 17 receptors thus far identified.	Chemokines activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power, Humana Press Inc., Totowa, NJ	Soluble CXCR4B receptor polypeptides may be useful for inhibiting chemokine activities and viral infection.
Interferon gamma-inducible protein (IP-10)	GeneSeq Accession W96709	US5871723	Chemokines area family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~ 17 receptors thus far identified.	Chemokines activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power, Humana Press Inc., Totowa, NJ	Angiogenesis, Cancer, Inflammatory and Immune disorders, Cardio-Vascular disorders, Musco-skeletal disorders

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
A monokine induced by gamma-interferon (MIG)	GeneSeq Accession W96710	US5871723	Chemokines area family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~ 17 receptors thus far identified.	Chemokines activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power, Humana Press Inc., Totowa, NJ	Angiogenesis, Cancer, Inflammatory and Immune disorders, Cardio-Vascular disorders, Musco-skeletal disorders
Interleukin-8 (IL-8) protein.	GeneSeq Accession W96711	US5871723	Chemokines area family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~ 17 receptors thus far identified.	Chemokines activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power, Humana Press Inc., Totowa, NJ; and Holmes et al (1991) Science 253, 1278-80.	Angiogenesis, Cancer, Inflammatory and Immune disorders, Cardio-Vascular disorders, Musco-skeletal disorders

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
Epithelial neutrophil activating protein-78 (ENA-78)	GeneSeq Accession W96712	US5871723	Chemokines area family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~ 17 receptors thus far identified.	Chemokines activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power, Humana Press Inc., Totowa, NJ	Angiogenesis, Cancer, Inflammatory and Immune disorders, Cardio-Vascular disorders, Musco-skeletal disorders
Growth related oncogene-alpha (GRO-alpha).	GeneSeq Accession W96713	US5871723	Chemokines area family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~ 17 receptors thus far identified.	Chemokines activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power, Humana Press Inc., Totowa, NJ	Angiogenesis, Cancer, Inflammatory and Immune disorders, Cardio-Vascular disorders, Musco-skeletal disorders

<b>Therapeutic Protein X</b>	<b>Exemplary Identifier</b>	<b>PCT/Patent Reference</b>	<b>Biological Activity</b>	<b>Exemplary Activity Assay</b>	<b>Preferred Indication Y</b>
Growth related oncogene-beta (GRO-beta)	GeneSeq Accession W96714	US5871723	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~ 17 receptors thus far identified	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power, © Humana Press Inc., Totowa, NJ	Angiogenesis, Cancer, Inflammatory and Immune disorders, Cardio-Vascular disorders, Musco-skeletal disorders
Growth related oncogene-gamma (GRO-gamma)	GeneSeq Accession W96715	US5871723	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~ 17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power, © Humana Press Inc., Totowa, NJ	Angiogenesis, Cancer, Inflammatory and Immune disorders, Cardio-Vascular disorders, Musco-skeletal disorders



<b>Therapeutic Protein X</b>	<b>Exemplary Identifier</b>	<b>PCT/Patent Reference</b>	<b>Biological Activity</b>	<b>Exemplary Activity Assay</b>	<b>Preferred Indication Y</b>
A platelet basic protein (PBP)	GeneSeq Accession W96716	US5871723	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power, © Humana Press Inc., Totowa, NJ	Angiogenesis, Cancer, Inflammatory and Immune disorders, Cardio-Vascular disorders, Musco-skeletal disorders
Connective tissue activating protein-III (CTAP-III)	GeneSeqAccession on S96717	US5871723	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power, © Humana Press Inc., Totowa, NJ	Angiogenesis, Cancer, Inflammatory and Immune disorders, Cardio-Vascular disorders, Musco-skeletal disorders

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
Beta-thromboglobulin protein (beta-TG)	GeneSeq Accession W96718	US5871723	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~ 17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power, © Humana Press Inc., Totowa, NJ	Angiogenesis, Cancer, Inflammatory and Immune disorders, Cardio-Vascular disorders, Musco-skeletal disorders
Neutrophil activating peptide-2 (NAP-2)	GeneSeq Accession W96719	US5871723	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~ 17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power, © Humana Press Inc., Totowa, NJ	Angiogenesis, Cancer, Inflammatory and Immune disorders, Cardio-Vascular disorders, Musco-skeletal disorders

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
Granulocyte chemotactic protein-2 (GCP-2)	GeneSeq Accession W96720	US5871723	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~ 17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power, © Humana Press Inc., Totowa, NJ	Angiogenesis, Cancer, Inflammatory and Immune disorders, Cardio-Vascular disorders, Musco-skeletal disorders
Human chemokine MIG-beta protein	GeneSeq Accession W90124	EP887409	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~ 17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power, © Humana Press Inc., Totowa, NJ	Immune disorders, viral, parasitic, fungal or bacterial infections, Cancer, autoimmune diseases or transplant rejection

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
Human ZCHEMO-8	GeneSeq Accession W82716	WO9854326	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~ 17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power, © Humana Press Inc., Totowa, NJ	Immune disorders, cancer, myelopietic disorders, autoimmune disorders and immunodeficiencies, Inflammatory and infectious diseases, Vascular disorders, wound healing
Human Act-2 protein	GeneSeq Accession W82717	WO9854326	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~ 17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power, © Humana Press Inc., Totowa, NJ	Immune disorders, cancer, myelopietic disorders, autoimmune disorders and immunodeficiencies, Inflammatory and infectious diseases, Vascular disorders, wound healing

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
Human SISD protein	GeneSeq Accession W82720	WO9854326	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols, Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ	Immune disorders, cancer, myelopoietic disorders, autoimmune disorders and immunodeficiencies, Inflammatory and infectious diseases, Vascular disorders, wound healing
Human M110 protein	GeneSeq Accession W82721	WO9854326	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols, Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ	Immune disorders, cancer, myelopoietic disorders, autoimmune disorders and immunodeficiencies, Inflammatory and infectious diseases, Vascular disorders, wound healing

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
Human M11A protein	GeneSeq Accession W82722	WO9854326	Chemokines area family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Mehtods of Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power © Humana Press Inc., Totowa, NJ	Immune disorders, cancer, myelopietic disorders, autoimmune disorders and immunodeficiencies, Inflammatory and infectious diseases, Vascular disorders, wound healing
Human CCC3 protein	GeneSeq Accession W82723	WO9854326	Chemokines area family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Mehtods of Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power © Humana Press Inc., Totowa, NJ	Immune disorders, cancer, myelopietic disorders, autoimmune disorders and immunodeficiencies, Inflammatory and infectious diseases, Vascular disorders, wound healing

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
A human L105 chemokine designated huL105_3.	GeneSeq Accession W87588	WO9856818	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods of Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power © Humana Press Inc., Totowa, NJ	Cancer, wound healing
A human L105 chemokine designated huL105_7.	GeneSeq Accession W87589	WO9856818	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods of Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power © Humana Press Inc., Totowa, NJ	Cancer, wound healing

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication
Human mature gro-alpha polypeptide used to treat sepsis	GeneSeq Accession W81498	WO9848828	Chemokines area family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods of Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power © Humana Press Inc., Totowa, NJ	Infectious diseases, sepsis
Human mature gro-gamma polypeptide used to treat sepsis	GeneSeq Accession W81500	WO9848828	Chemokines area family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods of Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power © Humana Press Inc., Totowa, NJ	Infectious diseases, sepsis



Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
Human thymus expressed chemokine TECK and TECK variant	GeneSeq Accessions B19607 and B19608	WO0053635	Chemokines area family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Mehtods of Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power © Humana Press Inc., Totowa, NJ	Inflammatory disorders, cancer, Immune and vascular disorders
Human chemokine SDF1alpha	GeneSeq Accession B15791	WO0042071	Chemokines area family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Mehtods of Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power © Humana Press Inc., Totowa, NJ	Autoimmune disorders, Immune, Vascular and Inflammatory disorders

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
Human chemokine GROalpha	GeneSeq Accession B15793	WO0042071	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot; T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ	Autoimmune disorders, Immune, Vascular and Inflammatory disorders
Human chemokine eotaxin	GeneSeq Accession B15794	WO0042071	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot; T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ	Autoimmune disorders, Immune, Vascular and Inflammatory disorders

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
Human chemokine MIG	GeneSeq Accession B15803	WO0042071	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~ 17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ	Autoimmune disorders, Immune, Vascular and Inflammatory disorders
Human chemokine PF4	GeneSeq Accession B15804	WO0042071	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~ 17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ	Autoimmune disorders, Immune, Vascular and Inflammatory disorders

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
Human chemokine I-309	GeneSeq Accession B15805	WO0042071	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~ 17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot; T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ	Autoimmune disorders, Immune, Vascular and Inflammatory disorders
Human chemokine HCC-1	GeneSeq Accession B15806	WO0042071	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~ 17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot; T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ	Autoimmune disorders, Immune, Vascular and Inflammatory disorders

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
Human chemokine C10	GeneSeq Accession B15807	WO0042071	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~ 17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot; T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ	Autoimmune disorders, Immune, Vascular and Inflammatory disorders
Human chemokine CCR-2	GeneSeq Accession B15808	WO0042071	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~ 17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot; T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ	Autoimmune disorders, Immune, Vascular and Inflammatory disorders

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
Human chemokine ENA-78	GeneSeq Accession B15809	WO0042071	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~ 17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot; T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ	Autoimmune disorders, Immune, Vascular and Inflammatory disorders
Human chemokine GRObeta	GeneSeq Accession B15810	WO0042071	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~ 17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot; T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ	Autoimmune disorders, Immune, Vascular and Inflammatory disorders

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
Human chemokine IP-10	GeneSeq Accession B15811	WO0042071	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~ 17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ	Autoimmune disorders, Immune, Vascular and Inflammatory disorders
Human chemokine SDF1beta	GeneSeq Accession B15812	WO0042071	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~ 17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ	Autoimmune disorders, Immune, Vascular and Inflammatory disorders

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
Human chemokine GRO alpha	GeneSeq Accession B15813	WO0042071	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~ 17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ	Autoimmune disorders, Immune, Vascular and Inflammatory disorders
Human chemokine MIP1beta	GeneSeq Accession B15831	WO0042071	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~ 17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ	Autoimmune disorders, Immune, Vascular and Inflammatory disorders



Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
A human C-C chemokine designated exodus	GeneSeq Accession B07939	US6096300	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~ 17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ	Cancer
Human chemokine L105_7	GeneSeq Accession Y96922	US6084071	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~ 17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ	Chemotaxis, Gene Therapy, Wound healing

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
Human chemokine L105_3	GeneSeq Accession Y96923	US6084071	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~ 17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ	Chemotaxis, Gene Therapy, Wound healing
Human secondary lymphoid chemokine (SLC)	GeneSeq Accession B01434	WO0038706	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~ 17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ	Cancer, Vascular and Immune disorders

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
Human non-ELR CXCR chemokine H174	GeneSeq Accession Y96310	WO0029439	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~ 17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ	Immune and Inflammatory disorders, Cancer, Haemostatic and thrombolytic activity
Human non-ELR CXCR chemokine IP10	GeneSeq Accession Y96311	WO0029439	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~ 17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ	Immune and Inflammatory disorders, Cancer, haemostatic and thrombolytic activity

<b>Therapeutic Protein X</b>	<b>Exemplary Identifier</b>	<b>PCT/Patent Reference</b>	<b>Biological Activity</b>	<b>Exemplary Activity Assay</b>	<b>Preferred Indication Y</b>
Human non-ELR CXC chemokine Mig	GeneSeq Accession Y96313	WO0029439	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ	Immune and inflammatory disorders, Cancer, haemostatic and thrombolytic activity
Human chemokine Ckbeta-7	GeneSeq Accession Y96280	WO0028035	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ	Cancer, wound healing, inflammatory and immunoregulatory disorders

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
Human chemokine MIP-1alpha	GeneSeq Accession Y96281	WO0028035	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ	Cancer, wound healing, inflammatory and immunoregulatory disorders
Human mature chemokine Ckbeta-7 (optionally truncated)	GeneSeq Accession Y96282	WO0028035	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ	Cancer, wound healing, inflammatory and immunoregulatory disorders

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
Human chemokine receptor CXCR3	GeneSeq Accession Y79372	WO0018431	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ	Soluble CXCR3 polypeptides may be useful for inhibiting chemokine activities and viral infection.
Human neurotactin chemokine like domain	GeneSeq Accession Y53259	US6043086	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to ~17 receptors thus far identified.	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ	Neurological disorders, Immune and respiratory disorders

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
Human CC type chemokine interleukin C	GeneSeq Accession Y57771	JP11302298	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to "17 receptors thus far identified	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ	Cancer and infectious diseases
Human CKbeta-9	GeneSeq Accession B50860	US6153441	Chemokines are a family of related small, secreted proteins involved in biological processes ranging from hematopoiesis, angiogenesis, and leukocyte trafficking. Members of this family are involved in a similarly diverse range of pathologies including inflammation, allergy, tissue rejection, viral infection, and tumor biology. The chemokines exert their effects by acting on a family of seven transmembrane G-protein-coupled receptors. Over 40 human chemokines have been described, which bind to "17 receptors thus far identified	Chemokine activities can be determined using assays known in the art: Methods in Molecular Biology, 2000, vol. 138: Chemokine Protocols. Edited by: A.E.I. Proudfoot, T.N.C. Wells, and C.A. Power. © Humana Press Inc., Totowa, NJ	Cancer, Auto-immune and inflammatory disorders, Cardiovascular disorders
Preproapolipoprotein "paris" variant	GeneSeq Accession W08602	WO9637608	Apoa-1 participates in the reverse transport of cholesterol from tissues to the liver for excretion by promoting cholesterol efflux from tissues and by acting as a cofactor for the lecithin cholesterol acyltransferase (lcat).	Lipid binding activity can be determined using assays known in the art, such as, for example, the Cholesterol Efflux Assays of Takahashi et al., P.N.A.S., Vol. 96, Issue 20, 11358-11363, September 28, 1999.	Useful for cardiovascular disorders, cholesterol disorders, and Hyperlipidaemia

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
Preproapolipoprotein "milano" variant		5,721,114	Apoa-1 participates in the reverse transport of cholesterol from tissues to the liver for excretion by promoting cholesterol efflux from tissues and by acting as a cofactor for the lecithin cholesterol acyltransferase (Lcat).	Lipid binding activity can be determined using assays known in the art, such as, for example, the Cholesterol Efflux Assays of Takahashi et al., P.N.A.S., Vol. 96, Issue 20, 11358-11363, September 28, 1999.	Useful for cardiovascular disorders, cholesterol disorders, and Hyperlipidaemia
Glycodelin-A; Progesterone-associated endometrial protein	GeneSeq Accession W00289	WO9628169	Naturally produced female contraceptive that is removed rapidly from the body following 2-3 days production. Uses include contraception	Glycodelin-A activity can be determined using the hemizona assay as described in Oehninger, S., Coddington, C.C., Hodgen, G.D., and Seppala, M (1995) Fertil. Steril. 63, 377-383.	Naturally derived contraceptive useful for the prevention of pregnancy.
NOGO-A	Genbank Accession CAB99248		NOGO polypeptides are potent inhibitors of neurite growth.	Inhibition of Neurite outgrowth. Antagonists to NOGO polypeptides may promote the outgrowth of neurites, thus inducing regeneration of neurons.	NOGO-A polypeptide antagonists are useful for the promotion of neural growth, which could be useful in the treatment of neural disorders and dysfunction due to degenerative diseases or trauma; useful in the treatment of neoplastic diseases of the CNS; induce regeneration of neurons or to promote the structural plasticity of the CNS.



Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
NOGO-B	Genbank Accession CAB99249		NOGO polypeptides are potent inhibitors of neurite growth.	Inhibition of Neurite outgrowth. Antagonists to NOGO polypeptides may promote the outgrowth of neurites, thus inducing regeneration of neurons.	NOGO-B polypeptide antagonists are useful for the promotion of neural growth, which could be useful in the treatment of neural disorders and dysfunction due to degenerative diseases or trauma; useful in the treatment of neoplastic diseases of the CNS; induce regeneration of neurons or to promote the structural plasticity of the CNS.
NOGO-C	Genbank Accession CAB99250		NOGO polypeptides are potent inhibitors of neurite growth.	Inhibition of Neurite outgrowth. Antagonists to NOGO polypeptides may promote the outgrowth of neurites, thus inducing regeneration of neurons.	NOGO-C polypeptide antagonists are useful for the promotion of neural growth, which could be useful in the treatment of neural disorders and dysfunction due to degenerative diseases or trauma; useful in the treatment of neoplastic diseases of the CNS; induce regeneration of neurons or to promote the structural plasticity of the CNS.

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
NOGO-66 Receptor	Genbank Accession AAG53612		NOGO polypeptides are potent inhibitors of neurite growth, and are thought to mediate their effects through the NOGO-66 Receptor.	Inhibition of Neurite outgrowth by mediating the biological effects of NOGO polypeptides. Soluble NOGO-66 receptor polypeptides may promote the outgrowth of neurites, thus inducing regeneration of neurons.	NOGO-66 receptor polypeptides are useful for the promotion of neural growth, which could be useful in the treatment of neural disorders and dysfunction due to degenerative diseases or trauma; useful in the treatment of neoplastic diseases of the CNS; induce regeneration of neurons or to promote the structural plasticity of the CNS.
Antibodies specific for collapsin		US5416197	These antibodies are useful for the promotion of neurite outgrowth	Collapsin activity, which is thought to inhibit the outgrowth of neurites, can be assayed in the presence of antibodies specific for collapsing using assays known in the art, such as, for example, the collapse assay disclosed by Luo et al., Cell 1993 Oct 22;75(2):217-27	Useful for the promotion of neural growth, which could be useful in the treatment of neural disorders and dysfunction due to degenerative diseases or trauma.
Humanized Anti-VEGF Antibodies, and fragments thereof		WO9845331	These agents have anti-inflammatory and anti-cancer applications	VEGF activity can be determined using assays known in the art, such as those disclosed in International Publication No. WO0045835, for example.	Promotion of growth and proliferation of cells, such as vascular endothelial cells. Antagonists may be useful as anti-angiogenic agents, and may be applicable for cancer
Humanized Anti-VEGF Antibodies, and fragments thereof		WO0029584	These agents have anti-inflammatory and anti-cancer applications	VEGF activity can be determined using assays known in the art, such as those disclosed in International Publication No. WO0045835, for example.	Promotion of growth and proliferation of cells, such as vascular endothelial cells. Antagonists may be useful as anti-angiogenic agents, and may be applicable for cancer

Therapeutic Protein X	Exemplary Identifier	PCT/Patent Reference	Biological Activity	Exemplary Activity Assay	Preferred Indication Y
Membrane bound proteins	GeneSeq Accession Y66631-Y66765	WO9963088	Cancer, Immune Disorders	These proteins can be used for linking bioactive molecules to cells and for modulating biological activities of cells, using the polypeptides for specific targeting. The polypeptide targeting can be used to kill the target cells, e.g. for the treatment of cancers. These proteins are useful for the treatment of immune system disorders.	Activities can be determined using assay known in the art, suchas, for example, the assays disclosed in International Publication No. WO0121658.
Secreted and Transmembrane polypeptides	GeneSeq Accession B44241-B44334	WO0053756	Cancer, Immune Disorders	These proteins can be used for linking bioactive molecules to cells and for modulating biological activities of cells, using the polypeptides for specific targeting. The polypeptide targeting can be used to kill the target cells, e.g. for the treatment of cancers. These proteins are useful for the treatment of immune system disorders.	Activities can be determined using assay known in the art, suchas, for example, the assays disclosed in International Publication No. WO0121658
Secreted and Transmembrane polypeptides	GeneSeq Accession Y41685-Y41774	WO9946281	Cancer, Immune Disorders	These proteins can be used for linking bioactive molecules to cells and for modulating biological activities of cells, using the polypeptides for specific targeting. The polypeptide targeting can be used to kill the target cells, e.g. for the treatment of cancers. These proteins are useful for the treatment of immune system disorders.	Activities can be determined using assay known in the art, suchas, for example, the assays disclosed in International Publication No. WO0121658

### **Delivery of a Drug or Therapeutic Protein to the inside of a Cell and/or across the Blood Brain Barrier (BBB)**

Within the scope of the invention, the modified transferrin fusion proteins may be used as a carrier to deliver a molecule or small molecule therapeutic complexed to the ferric ion of transferrin to the inside of a cell or across the blood brain barrier. In these  
5       embodiments, the Tf fusion protein will typically be engineered or modified to inhibit, prevent or remove glycosylation to extend the serum half-life of the fusion protein and/or therapeutic protein portion. The addition of a targeting peptide or, for example, a single chain antibody is specifically contemplated to further target the Tf fusion protein to a  
10       particular cell type, *e.g.*, a cancer cell.

In one embodiment, the iron-containing, anti-anemic drug, ferric-sorbitol-citrate complex is loaded onto a modified Tf fusion protein of the invention. Ferric-sorbitol-citrate (FSC) has been shown to inhibit proliferation of various murine cancer cells *in vitro* and cause tumor regression *in vivo*, while not having any effect on proliferation of non-  
15       malignant cells (Poljak-Blazi *et al.* (June 2000) *Cancer Biotherapy and Radiopharmaceuticals* (United States), 15/3:285-293).

In another embodiment, the antineoplastic drug adriamycin (Doxorubicin) and/or the chemotherapeutic drug bleomycin, both of which are known to form complexes with ferric ion, is loaded onto a Tf fusion protein of the invention. In other embodiments, a salt  
20       of a drug, for instance, a citrate or carbonate salt, may be prepared and complexed with the ferric iron that is then bound to Tf. As tumor cells often display a higher turnover rate for iron; transferrin modified to carry at least one anti-tumor agent, may provide a means of increasing agent exposure or load to the tumor cells. (Demant, *E.J.*, (1983) *Eur. J. of Biochem.* 137/(1-2):113-118; Padbury *et al.* (1985) *J. Biol. Chem.* 260/13:7820-7823).

### **Pharmaceutical Formulations and Treatment Methods**

The modified fusion proteins of the invention may be administered to a patient in need thereof using standard administration protocols. For instance, the modified Tf fusion proteins of the present invention can be provided alone, or in combination, or in sequential  
30       combination with other agents that modulate a particular pathological process. As used herein, two agents are said to be administered in combination when the two agents are administered simultaneously or are administered independently in a fashion such that the agents will act at the same or near the same time.

The agents of the present invention can be administered via parenteral,  
35       subcutaneous, intravenous, intramuscular, intraperitoneal, transdermal and buccal routes.

For example, an agent may be administered locally to a site of injury via microinfusion. Alternatively, or concurrently, administration may be noninvasive by either the oral, inhalation, nasal, or pulmonary route. The dosage administered will be dependent upon the age, health, and weight of the recipient, kind of concurrent treatment, if any, frequency of treatment, and the nature of the effect desired.

The present invention further provides compositions containing one or more fusion proteins of the invention. While individual needs vary, determination of optimal ranges of effective amounts of each component is within the skill of the art. Typical dosages comprise about 1 pg/kg to about 100 mg/kg body weight. The preferred dosages for systemic administration comprise about 100 ng/kg to about 100 mg/kg body weight or about 100-200 mg of protein/dose. The preferred dosages for direct administration to a site via microinfusion comprise about 1 ng/kg to about 1 mg/kg body weight. When administered via direct injection or microinfusion, modified fusion proteins of the invention may be engineered to exhibit reduced or no binding of iron to prevent, in part, localized iron toxicity.

In addition to the pharmacologically active fusion protein, the compositions of the present invention may contain suitable pharmaceutically acceptable carriers comprising excipients and auxiliaries that facilitate processing of the active compounds into preparations which can be used pharmaceutically for delivery to the site of action.

Suitable formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form, for example, water-soluble salts. In addition, suspensions of the active compounds as appropriate oily injection suspensions may be administered. Suitable lipophilic solvents or vehicles include fatty oils, for example, sesame oil, or synthetic fatty acid esters, for example, ethyl oleate or triglycerides.

Aqueous injection suspensions may contain substances which increase the viscosity of the suspension include, for example, sodium carboxymethyl cellulose, sorbitol and dextran. Optionally, the suspension may also contain stabilizers. Liposomes can also be used to encapsulate the agent for delivery into the cell.

The pharmaceutical formulation for systemic administration according to the invention may be formulated for enteral, parenteral or topical administration. Indeed, all three types of formulations may be used simultaneously to achieve systemic administration of the active ingredient. Suitable formulations for oral administration include hard or soft gelatin capsules, pills, tablets, including coated tablets, elixirs, suspensions, syrups or inhalations and controlled release forms thereof.

In practicing the methods of this invention, the agents of this invention may be used alone or in combination, or in combination with other therapeutic or diagnostic agents. In certain preferred embodiments, the compounds of this invention may be co-administered along with other compounds typically prescribed for these conditions according to generally accepted medical practice. The compounds of this invention can be utilized *in vivo*, ordinarily in mammals, such as humans, sheep, horses, cattle, pigs, dogs, cats, rats and mice, or *in vitro*.

Modified fusion proteins of the present invention may be used in the diagnosis, prognosis, prevention and/or treatment of diseases and/or disorders relating to diseases and disorders of the endocrine system, the nervous system, the immune system, respiratory system, cardiovascular system, reproductive system, digestive system, diseases and/or disorders relating to cell proliferation, and/or diseases or disorders relating to the blood.

In yet other embodiments of the invention, modified Tf fusion proteins may be used in the diagnosis, prognosis, prevention and/or treatment of diseases and/or disorders relating to diseases and disorders known to be associated with or treatable by therapeutic protein moieties as known in the art and exemplified by PCT Patent Publication Nos. WO 01/79258, WO 01/77137, WO 01/79442, WO 01/79443, WO 01/79444 and WO 01/79480, all of which are herein incorporated by reference in their entirety. Accordingly, the present invention encompasses a method of treating a disease or disorder listed in the "Preferred Indication Y" column of Table 1 comprising administering to a patient in which such treatment, prevention or amelioration is desired a modified transferrin fusion protein of the invention that comprises a therapeutic protein portion corresponding to a therapeutic protein disclosed in the "Therapeutic Protein X" column of Table 1 in an amount effective to treat, prevent or ameliorate the disease or disorder.

In certain embodiments, a transferrin fusion protein of the present invention may be used to diagnose and/or prognose diseases and/or disorders.

Modified transferrin fusion proteins of the invention and polynucleotides encoding transferrin fusion proteins of the invention may be useful in treating, preventing, diagnosing and/or prognosing diseases, disorders, and/or conditions of the immune system. Moreover, fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention can be used as a marker or detector of a particular immune system disease or disorder.

In a preferred embodiment fusion proteins of the invention and/or polynucleotides encoding modified transferrin fusion proteins of the invention could be used as an agent to

boost immunoresponsiveness among immunodeficient individuals. In specific embodiments, fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention could be used as an agent to boost immunoresponsiveness among B cell and/or T cell immunodeficient individuals.

5           The modified transferrin fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention may be useful in treating, preventing, diagnosing, and/or prognosing autoimmune disorders. Many autoimmune disorders result from inappropriate recognition of self as foreign material by immune cells. This inappropriate recognition results in an immune response leading to the destruction of the  
10   host tissue. Therefore, the administration of fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention, that can inhibit an immune response, particularly the proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing autoimmune disorders.

          Modified transferrin fusion proteins of the invention and/or polynucleotides  
15   encoding transferrin fusion proteins of the invention may be useful in treating, preventing, prognosing, and/or diagnosing diseases, disorders, and/or conditions of hematopoietic cells. Transferrin fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention could be used to increase differentiation and proliferation of hematopoietic cells, including the pluripotent stem cells, in an effort to  
20   treat or prevent those diseases, disorders, and/or conditions associated with a decrease in certain (or many) types hematopoietic cells, including but not limited to, leukopenia, neutropenia, anemia, and thrombocytopenia.

          Alternatively, modified fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention could be used to increase  
25   differentiation and proliferation of hematopoietic cells, including the pluripotent stem cells, in an effort to treat or prevent those diseases, disorders, and/or conditions associated with an increase in certain (or many) types of hematopoietic cells, including but not limited to, histiocytosis.

          Allergic reactions and conditions, such as asthma (particularly allergic asthma) or  
30   other respiratory problems, may also be treated, prevented, diagnosed and/or prognosing and using modified fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention. Moreover, these molecules can be used to treat, prevent, prognose, and/or diagnose anaphylaxis, hypersensitivity to an antigenic molecule, or blood group incompatibility.

Additionally, modified fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention, may be used to treat, prevent, diagnose and/or prognose IgE-mediated allergic reactions. Such allergic reactions include, but are not limited to, asthma, rhinitis, and ecizema. In specific embodiments, fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention may be used to modulate IgE concentrations in vitro or in vivo.

Moreover, modified fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention have uses in the diagnosis, prognosis, prevention, and/or treatment of inflammatory conditions. For example, since fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention may inhibit the activation, proliferation, and/or differentiation of cells involved in an inflammatory response, these molecules can be used to prevent and/or treat chronic and acute inflammatory conditions. Such inflammatory conditions include, but are not limited to, for example, inflammation associated with infection (*e.g.*, septic shock, sepsis, or systemic inflammatory response syndrome), ischemia-reperfusion injury, endotoxin lethality, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine induced lung injury, inflammatory bowel disease, Crohn's disease, over production of cytokines (*e.g.*, TNF or IL-1.), respiratory disorders (*e.g.*, asthma and allergy); gastrointestinal disorders (*e.g.*, inflammatory bowel disease); cancers (*e.g.*, gastric, ovarian, lung, bladder, liver, and breast); CNS disorders (*e.g.*, multiple sclerosis; ischemic brain injury and/or stroke, traumatic brain injury, neurodegenerative disorders (*e.g.*, Parkinson's disease and Alzheimer's disease); AIDS-related dementia; and prion disease); cardiovascular disorders (*e.g.*, atherosclerosis, myocarditis, cardiovascular disease, and cardiopulmonary bypass complications); as well as many additional diseases, conditions, and disorders that are characterized by inflammation (*e.g.*, hepatitis, rheumatoid arthritis, gout, trauma, pancreatitis, sarcoidosis, dermatitis, renal ischemia-reperfusion injury, Grave's disease, systemic lupus erythematosus, diabetes mellitus, and allogenic transplant rejection).

Because inflammation is a fundamental defense mechanism, inflammatory disorders can effect virtually any tissue of the body. Accordingly, modified fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention, have uses in the treatment of tissue-specific inflammatory disorders, including, but not limited to, adenitis, alveolitis, angiocholecystitis, appendicitis, balanitis, blepharitis, bronchitis, bursitis, carditis, cellulitis, cervicitis, cholecystitis, chondritis,



cochitis, colitis, conjunctivitis, cystitis, dermatitis, diverticulitis, encephalitis, endocarditis, esophagitis, eustachitis, fibrositis, folliculitis, gastritis, gastroenteritis, gingivitis, glossitis, hepatosplenitis, keratitis, labyrinthitis, laryngitis, lymphangitis, mastitis, media otitis, meningitis, metritis, mucitis, myocarditis, myositis, myringitis, 5 nephritis, neuritis, orchitis, osteochondritis, otitis, pericarditis, peritendonitis, peritonitis, pharyngitis, phlebitis, poliomyelitis, prostatitis, Pulpitis, retinitis, rhinitis, salpingitis, scleritis, sclerochoroiditis, scrotitis, sinusitis, spondylitis, steatitis, stomatitis, synovitis, syringitis, tendonitis, tonsillitis, urethritis, and vaginitis.

In specific embodiments, modified fusion proteins of the invention and/or 10 polynucleotides encoding transferrin fusion proteins of the invention, are useful to diagnose, prognose, prevent, and/or treat organ transplant rejections and graft-versus-host disease. Organ rejection occurs by host immune cell destruction of the transplanted tissue through an immune response. Similarly, an immune response is also involved in GVHD, but, in this case, the foreign transplanted immune cells destroy the host tissues.

15 Polypeptides, antibodies, or polynucleotides of the invention, and/or agonists or antagonists thereof, that inhibit an immune response, particularly the activation, proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing organ rejection or GVHD.

In another specific embodiment, modified transferrin fusion proteins of the 20 invention and/or polynucleotides encoding transferrin fusion proteins of the invention are used as an adjuvant to enhance anti-viral immune responses. Anti-viral immune responses that may be enhanced using the compositions of the invention as an adjuvant, include virus and virus associated diseases or symptoms described herein or otherwise known in the art. In specific embodiments, the compositions of the invention are used as an adjuvant to 25 enhance an immune response to a virus, disease, or symptom selected from the group consisting of AIDS, meningitis, Dengue, EBV, and hepatitis (*e.g.*, hepatitis B). In another specific embodiment, the compositions of the invention are used as an adjuvant to enhance an immune response to a virus, disease, or symptom selected from the group consisting of: HIV/AIDS, respiratory syncytial virus, Dengue, rotavirus, Japanese B encephalitis, 30 influenza A and B, parainfluenza, measles, cytomegalovirus, rabies, Junin, Chikungunya, Rift Valley Fever, herpes simplex, and yellow fever.

In another specific embodiment, modified transferrin fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention are used as an adjuvant to enhance anti-bacterial or anti-fungal immune responses. Anti-

bacterial or anti-fungal immune responses that may be enhanced using the compositions of the invention as an adjuvant, include bacteria or fungus and bacteria or fungus associated diseases or symptoms described herein or otherwise known in the art. In specific embodiments, the compositions of the invention are used as an adjuvant to enhance an immune response to a bacteria or fungus, disease, or symptom selected from the group consisting of tetanus, Diphtheria, botulism, and meningitis type B.

In another specific embodiment, the compositions of the invention are used as an adjuvant to enhance an immune response to a bacteria or fungus, disease, or symptom selected from the group consisting of *Vibrio cholerae*, *Mycobacterium leprae*, *Salmonellatyphi*, *Salmonella paratyphi*, *Meisseria meningitidis*, *Streptococcus pneumoniae*, Group B streptococcus, *Shigella* spp., Enterotoxigenic *Escherichia coli*, Enterohemorrhagic *E. coli*, and *Borrelia burgdorferi*.

In another specific embodiment, modified transferrin fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention are used as an adjuvant to enhance anti-parasitic immune responses. Anti-parasitic immune responses that may be enhanced using the compositions of the invention as an adjuvant, include parasite and parasite associated diseases or symptoms described herein or otherwise known in the art. In specific embodiments, the compositions of the invention are used as an adjuvant to enhance an immune response to a parasite. In another specific embodiment, the compositions of the invention are used as an, adjuvant to enhance an immune response to *Plasmodium* (malaria) or *Leishmania*.

In another specific embodiment, modified transferrin fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention may also be employed to treat infections diseases including silicosis, sarcoidosis, and idiopathic pulmonary fibrosis; for example, by preventing the recruitment and activation of mononuclear phagocytes.

In another specific embodiment, modified transferrin fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention are used as an antigen for the generation of antibodies to inhibit or enhance immune mediated responses against polypeptides of the invention.

In one embodiment, modified transferrin fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention are administered to an animal (*e.g.*, mouse, rat, rabbit, hamster, guinea pig, pigs, micro-pig, chicken, camel, goat, horse, cow, sheep, dog, cat non-human primate, and human, most preferably human)

to boost the immune system to produce increased quantities, of one or more antibodies (*e.g.*, IgG, IgA, IgM, and IaE), to induce higher affinity antibody production and immunoglobulin class switching (*e.g.*, IgG, IgA, IgM, and IaE), and/or to increase an immune response.

5           In another embodiment, modified transferrin fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention are used in one or more of the applications described herein, as they may apply to veterinary medicine.

10           In another specific embodiment, modified transferrin fusion proteins of the invention, and/or polynucleotides encoding transferrin fusion proteins of the invention are used as a means of blocking various aspects of immune responses to foreign agents or self. Examples of diseases or conditions in which blocking of certain aspects of immune responses may be desired include autoimmune disorders such as lupus, and arthritis, as well as immunoresponsiveness to skin allergies, inflammation, bowel disease, injury, and  
15           diseases/disorders associated with pathogens.

          In another specific embodiment, modified transferrin fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention are used as a therapy for preventing the B cell proliferation and Ig secretion associated with autoimmune diseases such as idiopathic thrombocytopenic purpura, systemic lupus  
20           erythematosus and multiple sclerosis.

          In another specific embodiment, modified transferrin fusion proteins or polynucleotides encoding transferrin fusion proteins of the invention are used as an inhibitor of B and/or T cell migration in endothelial cells. This activity disrupts tissue architecture or cognate responses and is useful, for example in disrupting immune  
25           responses, and blocking sepsis.

          In another specific embodiment, modified transferrin fusion proteins of the invention, and/or polynucleotides encoding transferrin fusion proteins of the invention are used as a therapy for chronic hypergammaglobulinemia evident in such diseases as monoclonal gammopathy of undetermined significance (MGUS), Waldenstrom's disease,  
30           related idiopathic monoclonal gammopathies, and plasmacytomas.

          Another specific embodiment, modified transferrin fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention may be employed for instance to inhibit polypeptide chemotaxis and activation of macrophages and their precursors, and of neutrophils, basophils, B lymphocytes and some T-cell

subsets, *e.g.*, activated and CD8 cytotoxic T cells and natural killer cells, in certain autoimmune and chronic inflammatory and infective diseases. Examples of autoimmune diseases are described herein and include multiple sclerosis, and insulin-dependent diabetes.

5           In another specific embodiment, modified transferrin fusion proteins of the invention and/or polynucleotides encoding transferrin fusion protein of the invention may also be employed for treating atherosclerosis, for example, by preventing monocyte infiltration in the artery wall.

10           In another specific embodiment, modified transferrin fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention may be employed to treat adult respiratory distress syndrome (ARDS).

15           In another specific embodiment, modified transferrin fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention may be useful for stimulating wound and tissue repair, stimulating angiogenesis, and/or stimulating the repair of vascular or lymphatic diseases or disorders. Additionally, fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention may be used to stimulate the regeneration of mucosal surfaces.

20           In a specific embodiment, modified transferrin fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention are used to diagnose, prognose, treat, and/or prevent a disorder characterized by primary or acquired immunodeficiency, deficient serum immunoglobulin production, recurrent infections, and/or immune system dysfunction. Moreover, modified fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention may be used to treat or prevent infections of the joints, bones, skin, and/or parotid glands, blood-borne  
25           infections (*e.g.*, sepsis, meningitis, septic arthritis, and/or osteomyelitis), autoimmune diseases (*e.g.*, those disclosed herein), inflammatory disorders, and malignancies, and/or any disease or disorder or condition associated with these infections, diseases, disorders and/or malignancies) including, but not limited to, CVID, other primary immune deficiencies, HIV disease, CLL, recurrent bronchitis, sinusitis, otitis media, conjunctivitis,  
30           pneumonia, hepatitis, meningitis, herpes zoster (*e.g.*, severe herpes zoster), and/or pneumocystis carinii. Other diseases and disorders that may be prevented, diagnosed, prognosed, and/or treated with fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention include, but are not limited to, HIV

infection, HTLV-BLV infection, lymphopenia, phagocyte bactericidal dysfunction anemia, thrombocytopenia, and hemoglobinuria.

In a specific embodiment, modified transferrin fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention may be used to diagnose, prognose, prevent, and/or treat cancers or neoplasms including immune cell or immune tissue-related cancers or neoplasms. Examples of cancers or neoplasms that may be prevented, diagnosed, or treated by fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention include, but are not limited to, acutemyelogenous leukemia, chronic myelogenous leukemia, Hodgkin's disease, non-Hodgkin's lymphoma, acute lymphocytic anemia (ALL) Chronic lymphocyte leukemia, plasmacytomas, multiple myetoma, Burkitt's lymphoma, EBV transformed diseases, and/or diseases and disorders described in the section entitled "Hyperproliferative Disorders" elsewhere herein.

In another specific embodiment, modified transferrin fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention are used as a therapy for decreasing cellular proliferation of Large B-cell Lymphomas.

In specific embodiments, the compositions of the invention are used as an agent to boost immunoresponsiveness among B cell immunodeficient individuals, such as, for example, an individual who has undergone a partial or complete splenectomy.

The modified transferrin fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention may be used to modulate homeostatic (the stopping of bleeding) or thrombolytic (clot dissolving) activity. For example, by increasing homeostatic or thrombolytic activity, fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention could be used to treat or prevent blood coagulation diseases, disorders, and/or conditions (*e.g.*, afibrinogenemia, factor deficiencies, hemophilia), blood platelet diseases, disorders, and/or conditions (*e.g.* thrombocytopenia), or wounds resulting from trauma, surgery, or other causes. Alliteratively, fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention that can decrease hemostatic or thrombolytic activity could be used to inhibit or dissolve clotting. These molecules could be important in the treatment or prevention of heart attacks (infarction), strokes, or scarring.

In specific embodiments, the modified transferrin fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention may be used to prevent diagnose, prognose, and/or treat thrombosis, arteria thrombosis, venous

thrombosis, thromboembolism, pulmonary embolism, atherosclerosis, myocardial infarction, transient ischenuc attack, unstable angina. In specific embodiments, the transferrin fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention maybe used for the prevention of occulsion of saphenous grafts, for reducing the risk of periprocedural thrombosis as might accompany angioplasty procedures, for reducing the risk of stroke in patients with atrial fibrillation including nonrheumatic atria fibrillation, for reducing the risk of embolism associated with mechanical heart valves and/or mitral valves disease. Other uses for the modified transferrin fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention, include, but are not limited to, the prevention of occlusions in extrcorporeal devices (*e.g.*, intravascular canals, vascular access shunts in hemodialysis patients, hemodialysis machines, and cardiopulmonary bypass machines).

In another embodiment, modified transferrin fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention, may be used to prevent, diagnose, prognose, and/or treat diseases and disorders of the blood and/or blood forming organs associated with the tissue(s) in which the polypeptide of the invention is expressed.

The modified fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention may be used to modulate hematopoietic activity (the formation of blood cells). For example, the transferrin fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention may be used to increase the quantity of all or subsets of blood cells, such as, for example, erythrocytes, lymphocytes (B or T cells), myeloid cells (*e.g.*, basophfis, eosinophitis, neutrophls, mast cells, macrophages) and platelets. The ability to decrease the quantity of blood cells or subsets of blood cells may be useful in the prevention, detection, diagnosis, and/or treatment of anemias and leukopenias described below. Alternatively, the modified transferrin fusion proteins, of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention maybe used to decrease the quantity of all or subsets of blood cells, such as, for example, erythrocytes, lymphocytes (B or T cells), myeloid cells (*e.g.*, basophils, eosinoptifis, neutrophils, mast cells, macrophages) and platelets. The ability to decrease the quantity of blood cells or subsets of blood cells may be useful in the prevention, detection, diagnosis, and/or treatment of leukocytoses, such as, for example eosinophilia. The modified fusion proteins of the invention and/or polynucleotides

encoding transferrin fusion proteins of the invention may be used to prevent, treat, or diagnose blood dyscrasia.

Anemias are conditions in which the number of red blood cells or amount of hemoglobin (the protein that carries oxygen) in them is below normal. Anemia may be caused by excessive bleeding, decreased red blood cell production, or increased red blood cell destruction (hemolysis). The modified transferrin fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention may be useful in treating, preventing, and/or diagnosing anemias. Anemias that may be treated prevented or diagnosed by the transferrin fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention include iron deficiency anemia, hypochromic anemia, microcytic anemia, chlorosis, hereditary sideroblastic anemia, idiopathic acquired sideroblastic anemia, red cell aplasia, megaloblastic anemia (*e.g.*, pernicious anemia, (vitamin B12 deficiency) and folic acid deficiency anemia), aplastic anemia, hemolytic anemias (*e.g.*, autoimmune hemolytic anemia, microangiopathic hemolytic anemia, and paroxysmal nocturnal hemoglobinuria). The modified transferrin fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention may be useful in treating, preventing, and/or diagnosing anemias associated with diseases including but not limited to, anemias associated with systemic lupus erythematosus, cancers, lymphomas, chronic renal disease, and enlarged spleens. The transferrin fusion proteins of the and/or polynucleotides encoding transferrin fusion proteins of the invention may be useful in treating, preventing, and/or diagnosing anemia arising from drug treatments such as anemias associated with methyldopa, dapsone, and/or sulfa drugs. Additionally, modified fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention maybe useful in treating, preventing, and/or diagnosing anemias associated with abnormal red blood cell architecture including but not limited to, hereditary spherocytosis, hereditary elliptocytosis, glucose-6-phosphate dehydrogenase deficiency, and sickle cell anemia.

The modified transferrin fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention may be useful in treating, preventing, and/or diagnosing hemoglobin abnormalities, (*e.g.*, those associated with sickle cell anemia, hemoglobin C disease, hemoglobin S-C disease, and hemoglobin E disease). Additionally, the transferrin fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention may be useful in diagnosing,

preventing, and/or prognosing in treating thalassemias, including, but not limited to, major and minor forms of alpha-thalassemia and beta-thalassemia.

In another embodiment, the modified transferrin fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention may be useful in diagnosing, prognosing, preventing, and/or treating bleeding disorders including, but not limited to, thrombocytopenia (*e.g.*, idiopathic thrombocytopenic purpura, and thrombotic thrombocytopenic purpura), Von Willebrand's disease, hereditary platelet disorders (*e.g.*, storage pool disease such as Chediak-Higashi and Hermansky-Pudlak syndromes, thromboxane A2 dysfunction, thromboasthenia, and Bernard-Soulier syndrome), hemolyticuremic syndrome, hemophelias such as hemophilia A or Factor V-11 deficiency and Christmas disease or Factor IX deficiency, Hereditary Hemorrhagic Telangiectasia, also known as Rendu-Osler-Webe syndrome, allergic purpura (Henoch Schonlein purpura) and disseminated intravascular coagulation.

In other embodiments, the modified transferrin fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention may be useful as an agent to increase cytokine production.

Hyperproliferative disorders in certain embodiments, fusion proteins of the invention, and/or polynucleotides encoding transferrin fusion proteins of the invention can be used to treat or detect hyperproliferative disorders, including neoplasms. Transferrin fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention may inhibit the proliferation of the disorder through direct or indirect interactions. Alternatively, fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention may proliferate other cells which can inhibit the hyperproliferative disorder.

For example, by increasing an immune response, particularly increasing antigenic qualities of the hyperproliferative disorder or by proliferating, differentiating, or mobilizing T-cells, hyperproliferative disorders can be treated. This immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response. Alternatively, decreasing an immune response may also be a method of treating hyperproliferative disorders, such as a chemotherapeutic agent.

Examples of hyperproliferative disorders that can be treated or detected by modified fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention include, but are not limited to neoplasms located in the: colon, abdomen, bone, breast, digestive system, liver, pancreas, peritoneum, endocrine



glands (adrenal, parathyroid, pituitary, testicles, ovary, thymus, thyroid), eye, head and neck, nervous (central and peripheral), lymphatic system, pelvis, skin, soft tissue, spleen, thorax, and urogenital tract.

Similarly, other hyperproliferative disorders can also be treated or detected by modified fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention. Examples of such hyperproliferative disorders include, but are not limited to Acute Childhood Lymphoblastic Leukemia; Acute Lymphoblastic Leukemia, Acute Lymphocytic Leukemia, Acute Myeloid Leukemia, Adrenocortical Carcinoma, Adult (Primary) Hepatocellular Cancer, Adult (Primary) Liver Cancer, Adult Acute Lymphocytic Leukemia, Adult Acute Myeloid Leukemia, Adult Hodgkin's Disease, Adult Hodgkin's Lymphoma, Adult Lymphocytic Leukemia, Adult Non-Hodgkin's Lymphoma, Adult Primary Liver Cancer, Adult Soft Tissue Sarcoma, AIDS-Related Lymphoma, AIDS-Related Malignancies, Anal Cancer, Astrocytoma, Bile Duct Cancer, Bladder Cancer, Bone Cancer, Brain Stem Glioma, Brain Tumors, Breast Cancer, Cancer of the Renal Pelvis and Ureter, Central Nervous System (Primary) Lymphoma, Central Nervous System Lymphoma, Cerebellar Astrocytoma, Cerebral Astrocytoma, Cervical Cancer, Childhood (Primary) Hepatocellular Cancer, Childhood (Primary) Liver Cancer, Childhood Acute Lymphoblastic Leukemia, Childhood Acute Myeloid Leukemia, Childhood Brain Stem Glioma, Childhood Cerebellar Astrocytoma, Childhood Cerebral Astrocytoma, Childhood Extracranial Germ Cell Tumors, Childhood Hodgkin's Disease, Childhood Hodgkin's Lymphoma, Childhood Hypothalamic and Visual Pathway Glioma, Childhood Lymphoblastic Leukemia, Childhood Medulloblastoma, Childhood Non-Hodgkin's Lymphoma, Childhood Pineal and Supratentorial Primitive Neuroectodermal Tumors, Childhood Primary Liver Cancer, Childhood Rhabdomyosarcoma, Childhood Soft Tissue Sarcoma, Childhood Visual Pathway and Hypothalamic Glioma, Chronic Lymphocytic Leukemia, Chronic Myelogenous Leukemia, Colon Cancer, Cutaneous T-Cell Lymphoma, Endocrine Pancreas Islet Cell Carcinoma. Endometrial Cancer, Ependymoma, Epithelial Cancer, Esophageal Cancer, Ewing's Sarcoma and Related Tumors, Exocrine Pancreatic Cancer, Extracranial Germ Cell Tumor, Extragonadal Germ Cell Tumor, Extrahepatic Bile Duct Cancer, Eye Cancer, Female Breast Cancer, Gaucher's Disease, Gallbladder Cancer, Gastric Cancer, Gastrointestinal Carcinoid Tumor, Gastrointestinal Tumors, Germ Cell Tumors, Gestational Trophoblastic Tumor, Hairy Cell Leukemia, Head and Neck Cancer, Hepatocellular Cancer, Hodgkin's Disease, Hodgkin's Lymphoma, Hypergammaglobulinemia, Hypopharyngeal Cancer, Intestinal Cancers,

Intraocular Melanoma, Islet Cell Carcinoma, Islet Cell Pancreatic Cancer, Kaposi's Sarcoma, Kidney Cancer, Laryngeal Cancer, Lip and Oral Cavity Cancer, Liver Cancer, Lung Cancer, Lympho proliferative Disorders, Macroglobulinemia, Male Breast Cancer, Malignant Mesothelioma, Malignant Thymoma, Medulloblastoma, Melanoma, Mesothelioma, Metastatic Occult Primary Squamous Neck Cancer, Metastatic Primary Squamous Neck Cancer, Metastatic Squamous Neck Cancer, Multiple Myeloma, Multiple Myeloma/Plasma Cell Neoplasm, Myelodysplastic Syndrome, Myelogenous Leukemia, Myeloid Leukemia, Myeloproliferative Disorders, Nasal Cavity and Paranasal Sinus Cancer, Nasopharyngeal Cancer, Neuroblastoma, Non-Hodgkin's Lymphoma During Pregnancy, Nonmelanoma Skin Cancer, Non-Small Cell Lung Cancer, Occult Primary Metastatic Squamous Neck Cancer, Oropharyngeal Cancer, Osteo/Malignant Fibrous Sarcoma, Osteosarcoma/Malignant Fibrous Histiocytoma, Osteosarcoma/Malignant Fibrous Histiocytoma of Bone, Ovarian Epithelial Cancer, Ovarian Germ Cell Tumor, Ovarian Low Malignant Potential Tumor, Pancreatic Cancer, Paraproteinemias, Purpura, Parathyroid, Cancer, Penile Cancer, Pheochromocytoma, Pituitary Tumor, Plasma Cell Neoplasm/Multiple Myeloma, Primary Central Nervous System Lymphoma, Primary Liver Cancer, Prostate Cancer, Rectal Cancer, Renal Cell Cancer, Renal Pelvis and Ureter Cancer, Retinoblastoma, Rhabdomyosarcoma, Salivary Gland Cancer, Sarcoidosis Sarcomas, Sezary Syndrome, Skin Cancer, Small Cell Lung Cancer, Small Intestine Cancer, Soft Tissue Sarcoma, Squamous Neck Cancer, Stomach Cancer, Supratentorial Primitive Neuroectodermal and Pineal Tumors, T-Cell Lymphoma, Testicular Cancer, Thymoma, Thyroid Cancer, Transitional Cell Cancer of the Renal Pelvis and Ureter, Transitional Renal Pelvis and Ureter Cancer, Trophoblastic Tumors, Ureter and Renal Pelvis Cell Cancer, Urethral Cancer, Uterine Cancer, Uterine Sarcoma, Vaginal Cancer, Visual Pathway and Hypothalamic Glioma, Vulvar Cancer, Waldenstrom's Macroglobulinemia, Wilm's Tumor, and any other hyperproliferative disease, besides neoplasia, located in an organ system listed above.

In another preferred embodiment, modified transferrin fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention are used to, diagnose, prognose, prevent, and/or treat premalignant conditions and to prevent progression to a neoplastic or malignant state, including but not limited to those disorders described above. Such uses are indicated in conditions known or suspected of preceding progression to neoplasia or cancer, in particular, where non-neoplastic cell growth is consisting of hyperplasia, metaplasia, or most particularly, dysplasia has occurred (for

review of such abnormal growth conditions, see Robbins. and Angell, 1976, Basic Pathology, 2d Ed. W. B. Saunders Co., Philadelphia, pp. 68-79).

Hyperplasia is a form of controlled cell proliferation, involving an increase in cell number in a tissue or organ, without, significant alteration in structure or function.

5 Hyperplastic disorders which can be diagnosed, prognosed, prevented, and/or treated with fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention include, but are not limited to, angiofollicular mediastinal lymph node hyperplasia, angiolymphoid hyperplasia with eosinophilia, atypical melanocytic hyperplasia, basal cell hyperplasia, benign giant lymph node hyperplasia, cementum  
10 hyperplasia, congenital adrenal hyperplasia, congenital sebaceous hyperplasia, cystic hyperplasia, cystic hyperplasia of the breast, denture hyperplasia, ductal hyperplasia, endometrial hyperplasia, fibromuscular hyperplasia, foca epithelial hyperplasia, gingival hyperplasia, inflammatory fibrous hyperplasia, inflammatory papillary hyperplasia, intravascular papillary endothelial hyperplasia, nodular hyperplasia of prostate, nodular  
15 regenerative hyperplasia, pseudoepitheliomatous hyperplasia, senile sebaceous hyperplasia, and verrucous hyperplasia.

In another embodiment, modified transferrin fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention conjugated to a toxin or a radio active isotope, as described herein, may be used to treat cancers and  
20 neoplasms, including, but not limited to, those described herein. In a further preferred embodiment, transferrin fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention conjugated to a toxin or a radioactive isotope, as described herein, may be used to treat acute myelogenous leukemia.

Additionally, modified fusion proteins of the invention and/or polynucleotides  
25 encoding transferrin fusion proteins of the invention may affect apoptosis, and therefore, would be useful in treating a number of diseases associated with increased cell survival or the inhibition of apoptosis. For example, diseases associated with increased cell survival or the inhibition of apoptosis that could be diagnosed, prognosed, prevented, and/or treated by polynucleotides, polypeptides, and/or agonists or antagonists of the invention, include  
30 cancers (such as follicular- lymphomas, carcinomas with p53 mutations, and hormone-dependent tumors, including, but not limited to, colon cancer, cardiac tumors, pancreatic cancer, melanoma, retinoblastoma, glioblastoma, lung cancer, intestinal cancer, testicular cancer, stomach cancer, neuroblastoma, myxoma, inyoma, lymphoma, endothelioma, osteoblastoma, osteoclastoma, osteosarcoma, chondrosarcoma, adenoma, breast cancer,

prostrate cancer, Kaposi's sarcoma and ovarian cancer); autoimmune disorders such as, multiple sclerosis, Sjogren's syndrome, Hashimoto's thyroiditis, biliary cirrhosis, Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis and rheumatoid arthritis) and viral infections (such as herpes viruses, pox viruses and adenoviruses), inflammation, graft v. host disease, acute graft rejection, and chronic graft rejection.

In preferred embodiments, modified fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention are used to inhibit growth, progression, and/or metastasis of cancers, in particular those listed above.

Additional diseases or conditions associated with increased cell survival that could be diagnosed, prognosed, prevented, and/or treated by modified fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention, include but are not limited to, progression, and/or metastases of malignancies and related disorders such as leukemia (including acute leukemia (*e.g.*, acute lymphocytic leukemia, acute myelocytic leukemia (including myeloblastic, promyelocytic, myelomonocytic, monocytic, and erythroleukemia)) and chronic leukemia (*e.g.*, chronic myelocytic (granulocytic) leukemia and chronic lymphocytic leukemia)), polycythemia vera, lymphomas (*e.g.*, Hodgkin's disease and non-Hodgkin's disease), multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain disease, and solid tumors including, but not limited to, Sarcomas and, carcinomas such as fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovium, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilms' tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, meningioma, melanoma, neuroblastoma, and retinoblastoma.

Diseases associated with increased apoptosis that could be diagnosed, prognosed, prevented, and/or treated by modified fusion proteins of the invention and/or

polynucleotides encoding transferrin fusion proteins of the invention, include AIDS; neurodegenerative disorders (such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, retinitis pigmentosa, cerebral degeneration and brain tumor or prior associated disease); autoimmune disorders (such as, multiple sclerosis, Sjogren's syndrome, Hashimoto's thyroiditis, biliary cirrhosis, Behcet's disease, Crohn's disease, 5 polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis and rheumatoid arthritis) myelodysplastic syndromes (such as a plastic anemia), graft Y host disease, ischemic injury (such as that caused by myocardial infarction, stroke and reperfusion injury), liver injury (*e.g.*, hepatitis related liver injury, ischemia/reperfusion injury, cholestasis (bile duct injury) and liver cancer); toxin-induced liver disease (such as 10 that caused by alcohol), septic shock, cachexia and anorexia.

Another preferred embodiment utilizes polynucleotides encoding modified transferrin fusion proteins of the invention to inhibit aberrant cellular division, by gene therapy using the present invention, and/or protein fusions or fragments thereof.

15 Thus, the present invention provides a method for treating cell proliferative disorders by inserting into an abnormally proliferating cell a polynucleotide encoding modified transferrin fusion protein of the present invention, wherein said polynucleotide represses said expression.

Another embodiment of the present invention provides a method of treating cell 20 proliferative disorders in individuals comprising administration of one or more active gene copies of the present invention to an abnormally proliferating cell or cells.

The polynucleotides of the present invention may be delivered directly to cell proliferative disorderly disease sites in internal organs, body cavities, and the like by use of imaging devices used to guide an injecting needle directly to the disease site. The 25 polynucleotides of the present invention may also be administered to disease sites at the time of surgical intervention.

By cell proliferative disease is meant any human or animal disease or disorder, affecting any one or any combination of organs, cavities, or body parts, which is characterized by single or multiple local abnormal proliferations of cells, groups of cells, 30 or tissues, whether benign or malignant.

Any amount of the polynucleotides of the present invention may be administered as long as it has a biologically inhibiting effect on the proliferation of the treated cells.

Moreover, it is possible to administer more than one of the polynucleotides of the present invention simultaneously to the same site. By "biologically inhibiting" is meant

partial or total growth inhibition as well as decreases in the rate of proliferation or growth of the cells.

Modified transferrin fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention are useful in inhibiting the metastasis of proliferative cells or tissues. Inhibition may occur as a direct result of administering these transferrin fusion proteins and/or polynucleotides, or indirectly, such as activating the expression of proteins known to inhibit metastasis, for example alpha, integrins, (See, *e.g.*, Curr Top Microbiol Immunol 1998; 231:1 41, which is hereby incorporated by reference). Such therapeutic affects of the present invention may be achieved either alone, or in combination with small molecule drugs or adjuvants.

In another embodiment, the invention provides a method of delivering compositions containing the transferrin fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention to targeted cells expressing the a polypeptide bound by, that binds to, or associates with a modified transferrin fusion protein of the invention. Transferrin fusion proteins of the invention may be associated with heterologous polypeptides, heterologous nucleic acids, toxins, or prodrugs via hydrophobic, hydrophilic, ionic and/or covalent interactions.

Kidney diseases which can be diagnosed, prognosed, prevented, and/or treated with compositions of the invention include, but are not limited to, acute kidney failure, chronic kidney failure, atheroembolic renal failure, end-stage renal disease, inflammatory diseases of the kidney (*e.g.*, acute glomerulonephritis, post infectious glomerulonephritis, rapidly progressive glomerulonephritis, nephritic syndrome, membranous glomerulonephritis, familial nephritic syndrome, membrane proliferative glomerulonephritis and mesangial proliferative glomerulonephritis, chronic glomerulonephritis, acute tubulo intestinal nephritis, chronic tubulointerstitial nephritis, acute post-streptococcal glomerulonephritis(PSGN), pyelonephritis, lupus nephritis, chronic nephritis, interstitial nephritis, and post streptococcal glomerulonephritis), blood vessel disorders of the kidneys (*e.g.*, kidney infarction, atheroembolic kidney disease, cortical necrosis, malignant nephrosclerosis, renal vein thrombosis, renal under perfusion, renal retinopathy, renal ischemia-reperfusion, renal artery embolism and renal artery stenosis), and kidney disorders resulting form urinary tract disease (*e.g.*, pyelonephritis, hydronephrosis, urolithiasis (renal lithiasis, nephrolithiasis), reflux nephropathy, urinary tract infections, urinary retention, and acute or chronic unilateral obstructive uropathy). In addition, compositions of the invention can be used to diagnose, prognose, prevent, and/or

treat metabolic and congenital disorders of the kidney (*e.g.*, uremia, renal amyloidosis, renal osteodystrophy, renal tubular acidosis, renal glycosuria, nephrogenic diabetes insipidus, cystinuria, Fanconi's syndrome, renal fibrocystic osteosis (renal rickets), Hartnup disease, Bartter's syndrome, Liddle's syndrome, polycystic kidney disease, medullary cystic disease, medullary sponge kidney, Alport's syndrome, nail-patella syndrome, congenital nephritic syndrome, CRUSH syndrome, horseshoe kidney, diabetic nephropathy, nephrogenic diabetes insipidus, analgesic nephropathy, kidney stones, and membranous nephropathy), and autoimmune disorders of the kidney (*e.g.*, systemic lupus erythematosus (SLE), Good pasture syndrome, IgA nephropathy, and ICFM mesangial proliferative glomerulonephritis).

Compositions of the invention can also be used to diagnose, prognose, prevent, and/or treat sclerotic or necrotic disorders of the kidney (*e.g.*, glomerulosclerosis, diabetic nephropathy, focal segmental glomerulosclerosis (FSGS), necrotizing glomerulonephritis, and renal papillary necrosis), cancers of the kidney (*e.g.*, nephroma, hypemphroma, nephroblastoma, renal cell cancer, transitional cell cancer, renal adenocarcinoma, squamous cell cancer, and Wilm's tumor), and electrolyte imbalances (*e.g.*, nephrocalcinosis, pyuria, edema, hydronephritis, proteinuria, hyponatremia, hypematremia, hypokalemia, hyperkalemia, hypocalcemia, hypercalcemia, hypophosphatemia, and hyperphosphatemia).

Compositions of the invention may be administered using any method known in the art, including, but not limited to, direct needle injection at the delivery site, intravenous injection, topical administration, catheter infusion, biolistic injectors, particle accelerators, gel foam sponge depots, other commercially available depot materials, osmotic pumps, oral or suppository solid pharmaceutical formulations, decanting or topical applications during surgery, aerosol delivery. Such methods are known in the art. Compositions of the invention may be administered as part of a Therapeutic, described in more detail below.

Modified transferrin fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention, may be used to treat, prevent, diagnose, and/or prognose cardiovascular disorders, including, but not limited to, peripheral artery disease, such as limb ischemia.

Cardiovascular disorders, includes, but is not limited to, cardiovascular abnormalities, such as arterioarterial fistula, arteriovenous fistula, cerebral arteriovenous malformations, congenital heart defects, pulmonary atresia, and Scimitar Syndrome.

Congenital heart defects include, but are not limited to, aortic coarctation, cortriatriatum, coronary vessel anomalies, crisscross heart, dextrocardia, patent ductus arteriosus, Ebstein's anomaly, Eisenmenger complex, hypoplastic left heart syndrome, levocardia, tetralogy of fallot, transposition of great vessels, double outlet right ventricle, tricuspidatresia, persistent truncus arteriosus, and heart septal defects, such as aortopulmonary septald defect, endocardial cushion defects, Lutembacher's Syndrome, trilogy of Fallot, ventricular heart septal defects.

Cardiovascular disorders also include, but are not limited to, heart disease, such as amhythrias, carcinoid heart disease, high cardiac output, low cardiac output, cardiactamponade, endocarditis (including bacteria), heart aneurysm, cardiac arrest, congestive heart failure, congestive cardiomyopathy, paroxysmal dyspnea, cardiac edema, heart hypertrophy, congestive cardiomyopathy left ventricular hypertrophy, right ventricularhypertrophy, post-infarction heart rupture, ventricular septal ruoture, heart valve diseases myocardial diseases, myocardial ischemia, pericardial effusion, pericarditis (including constrictive and tuberculous), pricumopericardium, post pericardiotomy syndrome, pulmonary heart disease, rheumatic heart disease, ventricular dysfunction, hyperemia, cardiovascular pregnancy complications, Scimitar Syndrome, cardiovascular syphilis, and cardiovascular tuberculosis.

Arrhythmias include, but are not limited to, sinus arrhythmia, atrial fibrillation, atrial flutter, bradycardia, extrasystole, Adams-Stokes Syndrome, bundle-branch block, sinoatrial block, long QT syndrome, parasystole, Lown-Ganong-Levine Syndrome, Mahaim-type pre-excitation syndrome, Wolff-Parkinson-White syndrome, sick sinus syndrome, itachycardias, and ventricular fibrillation. Tachycardias include paroxysmal tachycardia, suprayentriculai tachycardia, accelerated idioventricular rhythm, atrioventricular nodal reentry tachyeardia, ectopic atrial tachycardia, ectopic junctional tachycardia, sinoattial nodalreentry tachycardia, sinus tachycardia, Torsades de Pointes, and ventricular tachycardia.

Heart valve diseases include, but are not limited to, aortic valve insufficiency aorticvalve stenosis, hear murmurs, aortic valve prolapse, neutral valve prolapse, tricuspid valve prolapse, mitral valve insufficiency, mitral valve stenosis, pulmonary atresia, pulmonary valve insufficiency, pulmonary valve stenosis, tricuspid atresia, tricuspid valve insufficiency, and tricuspid valve stenosis.

Myocardial diseases include, but are not limited to, alcoholic cardiomyopathy, congestive cardiomyopathy, hypertrophic cardiomyopathy, aortic subvalvular stenosis,



pulmonary subvalvular stenosis, restrictive cardiomyopathy, Chagas cardiomyopathy, endocardial fibroelastosis, endomyocardial fibrosis, Kearns Syndrome, myocardial reperfusion injury, and myocarditis.

Myocardial schemias include, but are not limited to, coronary disease, such as  
5 angina pectoris, coronary aneurysm, coronary arteriosclerosis, coronary thrombosis, coronary vasospasm, myocardial infarction, and myocardial stunning.

Cardiovascular diseases also include vascular diseases such as aneurysms, angiodyplasia, angiomas, bacillary angiomatosis, Hippel-Lindau Disease, Klippel  
Trenaunay Weber Syndrome, Sturge Weber Syndrome, angioneurotic edema, aortic  
10 diseases, Takayasu's Arthritis, aortitis, Leriche's Syndrome, arterial occlusive diseases, arthritis, arteritis, polyarteritis nodosa, cerebrovascular disorders, diabetic angiopathies, diabetic retinopathy, embolisms, thrombosis, erythromelalgia, hemorrhoids, hepatic veno-occlusive disease, hypertension, hypotension, ischemia, peripheral vascular diseases, phlebitis, pulmonary veno-occlusive disease, Raynaud's disease, CREST syndrome, retinal  
15 vein occlusion, Scimitar syndrome, superior vena cava syndrome, telangiectasia, ataxial telangiectasia, hereditary hemorrhagic telangiectasia, varicocele, varicose veins, varicose ulcer, vasculitis, and venous insufficiency.

Cerebrovascular disorders include, but are not limited to, cardio artery diseases, Respiratory Disorders Transferrin fusion proteins of the invention and/or polynucleotides  
20 encoding transferrin fusion proteins of the invention may be used to treat, prevent, diagnose, and/or prognose diseases and/or disorders of the respiratory system.

Diseases and disorders of the respiratory system include, but are not limited to, nasal vestibulitis, nonallergic rhinitis (*e.g.*, acute rhinitis, chronic rhinitis, atrophic rhinitis, vasomotor rhinitis), nasal polyps, and sinusitis, juvenile angiofibromas, cancer of the nose  
25 and juvenile papillomas, vocal cord polyps, nodules (singer's nodules), contact ulcers, vocal cord paralysis, laryngoceles, pharyngitis (*e.g.*, viral and bacterial), tonsillitis, tonsillar cellulitis, parapharyngeal abscess, laryngitis, laryngoceles, and throat cancers (*e.g.*, cancer of the nasopharynx, tonsil cancer, larynx cancer), lung cancer (*e.g.*, squamous cell carcinoma, small cell (oat cell) carcinoma, large cell carcinoma, and adenocarcinoma),  
30 allergic disorders (eosinophilic pneumonia, hypersensitivity pneumonitis (*e.g.*, extrinsic allergic alveolitis, allergic interstitial pneumonitis, organic dust pneumoconiosis, allergic bronchopulmonary aspergillosis, asthma, Wegener's granulomatosis (granulomatous vasculitis), Goodpasture's syndrome)), pneumonia (*e.g.*, bacterial pneumonia (*e.g.*, *Streptococcus pneumoniae* (pneumococcal pneumonia), *Staphylococcus*

aureus (staphylococcal pneumonia), Gram negative bacteria pneumonia (caused by, *e.g.*, Klebsiella and Pseudomonas spp.), Mycoplasma pneumoniae pneumonia, Hemophilus influenza pneumonia, Legionella pneumophila (Legionnaires' disease), and Chlamydia pneumoniae (Psittacosis), and viral pneumonia (*e.g.*, influenza, chickenpox (varicella).

Additional diseases and disorders of the respiratory system include, but are not limited to bronchiolitis, polio (poliomyelitis), croup, respiratory syncytial viral infection, mumps, erythema infectiosum (fifth disease), roseola infantum, progressive rubella panencephalitis, German measles, and subacute sclerosing panencephalitis), fungal pneumonia (*e.g.*, Histoplasmosis, Coccidioidomycosis, Blastomycosis, fungal infections in people with severely suppressed immune systems (*e.g.*, cryptococcosis, caused by Cryptococcus neoformans; aspergillosis, caused by Aspergillus spp.) candidiasis, caused by Candida; and mucormycosis)), Pneumocystis carinii (pneumocystis pneumonia), atypical pneumonias (*e.g.*, Mycoplasma and Chlamydia spp.), opportunistic infection pneumonia, nosocomial pneumonia, chemical pneumonitis, and aspiration pneumonia, pleural disorders (*e.g.*, pleurisy, pleural effusion, and pneumothorax (*e.g.*, simple spontaneous pneumothorax, complicated spontaneous pneumothorax, tension pneumothorax)), obstructive airway diseases (*e.g.*, asthma, chronic obstructive pulmonary disease (COPD), emphysema, chronic or acute bronchitis), occupational lung diseases (*e.g.*, silicosis, black lung (coal workers' pneumoconiosis), asbestosis, berylliosis, occupational asthma, byssinosis, and benign pneumoconiosis), Infiltrative Lung Disease (*e.g.*, pulmonary fibrosis (*e.g.*, fibrosing alveolitis, usual interstitial pneumonia), idiopathic pulmonary fibrosis, desquamate interstitial pneumonia, lymphoid interstitial pneumonia, histiocytosis (*e.g.*, Letterer-Siwe disease, Hand-Schüller-Christian disease, eosinophilic granuloma), idiopathic pulmonary hemosiderosis, sarcoidosis and pulmonary, alveolar proteinosis), Acute respiratory distress syndrome (also called, *e.g.*, adult respiratory distress syndrome), edema, pulmonary embolism, bronchitis (*e.g.*, viral, bacterial), bronchiectasis, atelectasis, lung abscess (caused by, *e.g.*, Staphylococcus aureus or Legionella pneumophila), and cystic fibrosis.

Cancers which may be treated with modified fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention include, but are not limited to solid tumors, including prostate, lung, breast, ovarian, stomach, pancreas, larynx, esophagus, testis, liver, parotid, biliary tract, colon, rectum, cervix, uterus, endometrium, kidney, bladder, thyroid cancer; primary tumors and metastases;

melanomas; glioblastoma; Kaposi's sarcoma; leiomyosarcoma; non-small cell lung cancer; colorectal cancer; advanced malignancies; and blood born tumors such as leukemia. For example, fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention may be delivered topically, in order to treat  
5 cancers such as skin cancer, head and neck tumors, breast tumors, and Kaposi's sarcoma.

Modified transferrin fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention may be useful, in treating other disorders, besides cancers, which involve angiogenesis. These disorders include, but are not limited to: benign tumors, for example hemangiomas, acoustic neuromas,  
10 neurofibromas, trachomas, and pyogenic granulomas; atherosclerotic plaques; ocular angiogenic diseases, for example, diabetic retinopathy, retinopathy of prematurity, macular degeneration, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, rubeosis, retinoblastoma, uveitis and Pterygia (normal blood vessel growth) of the eye; rheumatoid arthritis; psoriasis; delayed wound healing; endometriosis;  
15 vasculogenesis; granulations; hypertrophic scars (keloids); nonunion fractures; scleroderma; trachoma; vascular adhesions; myocardial angiogenesis; coronary collaterals; cerebral collaterals; arteriovenous malformations; ischemic limb angiogenesis; Osler-Webber Syndrome; plaque neovascularization; telangiectasia; hemophilic joints; angiofibroma; fibromuscular dysplasia; wound granulation; Crohn's disease; and  
20 atherosclerosis.

Thus, within one aspect of the present invention methods are provided for treating neovascular diseases of the eye.

Additionally, disorders which can be treated with modified fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention  
25 include, but are not limited to, hemangioma, arthritis, psoriasis, angiofibroma, atherosclerotic plaques, delayed wound healing, granulations hemophilic joints, hypertrophic scars, nonunion fractures, Osler-Weber syndrome, pyogenic granuloma, scleroderma, trachoma; and vascular adhesions.

Moreover, disorders and/or states, which can be treated, prevented, diagnosed,  
30 and/or prognosed with the modified transferrin fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention include, but are not limited to, solid tumors, blood born tumors such as leukemia, tumor metastasis, Kaposi's sarcoma, benign tumors, for example hemangiomas, acoustic neuromas, neurofibromas, trachomas, and pyogenic granulomas, rheumatoid arthritis, psoriasis, ocular angiogenic

diseases, for example, diabetic retinopathy, retinopathy of prematurity, macular degeneration, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, rubeosis, retinoblastoma, and uveitis, delayed wound healing, endometriosis, vasculogenesis, granulations, hypertrophic scars (keloids), nonunion fractures, scleroderma, trachoma, vascular adhesions, myocardial angiogenesis, coronary collaterals, cerebral collaterals, arteriovenous malformations, ischemic limb angiogenesis, Osler-Webber Syndrome, plaque neovascularization, telangiectasia, hemophilic joints, angiofibroma fibromuscular dysplasia, wound granulation, Crohn's disease, atherosclerosis, birth control agent by preventing vascularization required for embryo, implantation controlling menstruation, diseases that have angiogenesis as a pathologic consequence such as cat scratch disease (*Rochelium nuttallii*), ulcers (*Helicobacter pylori*), Bartonellosis and bacillary angiomatosis.

In one aspect of the birth control method, an amount of the compound sufficient to block embryo implantation is administered before or after intercourse and fertilization have occurred, thus providing an effective method of birth control, possibly a "morning after" method. Modified transferrin fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention may also be used in controlling menstruation or administered as either a peritoneal lavage fluid or for peritoneal implantation in the treatment of endometriosis.

Modified transferrin fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention may be utilized in a wide variety of surgical procedures.

Diseases associated with increased cell survival or the inhibition of apoptosis that could be treated, prevented, diagnosed, and/or prognosed using modified fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention, include cancers (such as follicular lymphomas, carcinomas with mutations, and hormone-dependent tumors, including, but not limited to colon cancer, cardiac tumors, pancreatic cancer, melanoma, retinoblastoma, glioblastoma, lung cancer, intestinal cancer, testicular cancer, stomach cancer, neuroblastoma, myxoma, myoma, lymphoma, endothelioma, osteoblastoma, osteoclastoma, osteosarcoma, chondrosarcoma, adenoma, breast cancer, prostate cancer, Kaposi's sarcoma and ovarian cancer); autoimmune disorders (such as, multiple sclerosis, Sjogren's syndrome, Hashimoto's thyroiditis, biliary cirrhosis, Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis and rheumatoid arthritis) and viral infections (such

as herpes viruses, pox viruses and adenoviruses), inflammation, graft v. host disease, acute graft rejection, and chronic graft rejection.

In preferred embodiments, modified fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention are used to inhibit growth, progression, and/or metasis of cancers, in particular those listed above.

Additional diseases or conditions associated with increased cell survival that could be treated or detected by modified fusion proteins of the invention and/or polynucleotides encoding, transferrin fusion proteins of the invention include, but are not limited to, progression, and/or metastases of malignances and related disorders such as leukemia (including acute leukemia (*e.g.*, acute lymphocytic leukemia, acute myelocytic leukemia (including myeloblastic, promyelocytic, myelomonocytic, monocytic, and erythroleukemia)) and chronic leukemia (*e.g.*, chronic myelocytic (granulocytic) leukemia and chronic lymphocytic leukemia)), polycythemia vera, lymphomas (*e.g.*, Hodgkin's disease and non-Hodgkin's disease), multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain disease, and solid tumors including, but not limited to, Sarcomas and carcinomas such as fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchiogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilms' tumor, cervical cancer, testicular tumor, Jung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, meningioma, melanoma, neuroblastoma, and retinoblastoma.

Diseases associated with increased apoptosis that could be treated, prevented, diagnosed, and/or prognosed using modified fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention, include, but are not limited to, AIDS; neurodegenerative disorders (such as Alzheimer's disease, Parkinson's disease, Amyotrophic lateral sclerosis, Retinitis pigmentosa, Cerebellar degeneration and brain tumor or prior associated disease); autoimmune disorders (such as, multiple

sclerosis, Sjogren's syndrome, Hashimoto's thyroiditis, biliary cirrhosis, Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis and rheumatoid arthritis) Myelodysplastic syndromes (such as aplastic anemia), graft v. host disease, ischemic injury (such as that caused, by myocardial

5 infarction, stroke and reperfusion injury), liver injury (e.g., hepatitis related liver injury, ischemia/reperfusion injury, cholestasis (bile duct injury) and liver cancer); toxin-induced liver disease (such as that caused by alcohol), septic shock, cachexia and anorexia.

In addition, modified fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention could be, used to treat or prevent the  
10 onset of diabetes mellitus. In patients with newly diagnosed Types 1 and 11 diabetes, where some islet cell function remains, fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention, could be used to maintain the islet function so as to alleviate, delay or prevent permanent manifestation of the disease. Also, fusion proteins of the invention and/or polynucleotides encoding  
15 transferrin fusion proteins of the invention could be used as an auxiliary in islet cell transplantation to improve or promote islet cell function.

The modified transferrin fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention may be used for the diagnosis and/or treatment of diseases, disorders, damage or injury of the brain and/or nervous system.

20 Nervous system disorders that can be treated with the compositions of the invention (e.g., fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention), limited to nervous systems include, but are not limited to, injuries, and diseases or disorders which result in either a disconnection of axons, a diminution or degeneration of neurons, or demyelination. Nervous system lesions which may be treated  
25 in a patient (including human and non-human mammalian patients) according to the methods of the invention, include but are not limited to, the following lesions of either the central (including spinal cord, brain) or peripheral nervous systems: (1) ischemic lesions, in which a lack of oxygen in a portion of the nervous system results in neuronal injury or death, including cerebral infarction or ischemia, or spinal cord infarction or ischemia; (2)  
30 traumatic lesions, including lesions caused by physical injury or associated with surgery, for example, lesions which sever a portion of the nervous system, or compression injuries; (3) malignant lesions, in which a portion of the nervous system is destroyed or injured by malignant tissue which is either a nervous system associated malignancy or a malignancy derived from nervous system tissue; (4) infectious lesions in which a portion of the

nervous system is destroyed or injured as a result of infection, for example, by an abscess or associated with infection by human immunodeficiency virus, herpes zoster, or herpes simplex virus or with Lyme disease, tuberculosis, or syphilis; (5) degenerative lesions, in which a portion of the nervous system is destroyed or injured as a result of a degenerative process including but not limited to, degeneration associated with Parkinson's disease, Alzheimer's disease, Huntington's chorea, or amyotrophic lateral sclerosis (ALS); (6) lesions associated with nutritional diseases or disorders, in which a portion of the nervous system is destroyed or injured by a nutritional disorder or disorder of metabolism including, but not limited to vitamin B 12 deficiency, folic acid deficiency, Wernicke disease, tobacco-alcohol amblyopic, Marchiafava-Blanzi disease (primary degeneration of the corpus callosum), and alcoholic cerebral degeneration; (7) neurological lesions associated with systemic diseases including, but not limited to diabetes (diabetic neuropathy, Bell's palsy), systemic lupus erythematosus, carcinoma, or sarcoidosis; (8) lesions caused by toxic substances including alcohol, lead, or particular, neurotoxins; and (9) demyelinated lesions in which a portion of the nervous system is destroyed or injured by a demyelinating disease including, but not limited to, multiple sclerosis, human immunodeficiency virus-associated myelopathy, transverse myelopathy or various etiologies, progressive multifocal leukoencephalopathy, and central pontine myelinolysis.

In one embodiment, the modified transferrin fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention are used to protect neural cells from the damaging effects of hypoxia. In a further preferred embodiment, the modified transferrin fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention are used to protect neural cells from the damaging effects of cerebral hypoxia.

In specific embodiments, motor neuron disorders that may be treated according to the invention include, but are not limited to, disorders such as infarction, infection, exposure to toxin, trauma, surgical damage, degenerative disease or malignancy that may affect motor neurons as well as other components of the nervous system, as well as disorders that selectively affect neurons such as amyotrophic lateral sclerosis, and including, but not limited to, progressive spinal muscular atrophy, progressive bulbar palsy, primary lateral sclerosis, infantile and juvenile muscular atrophy, progressive bulbar paralysis of childhood (Fazio-Londe syndrome), poliomyelitis and the post polio syndrome, and Hereditary Motor sensory Neuropathy (Charcot-Marie-Tooth Disease).

Further, modified fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention may play a role in neuronal survival; synapse formation; conductance; neural differentiation, etc. Thus, compositions of the invention (including fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention) may be used to diagnose and/or treat or prevent diseases or disorders associated with these roles, including, but not limited to, learning and/or cognition disorders. The compositions of the invention may also be useful in the treatment or prevention of neurodegenerative disease states and/or behavioral disorders. Such neurodegenerative disease states and/or behavioral disorders include, but are not limited to, Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception.

Examples of neurologic diseases which can be treated or detected with modified fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention include, brain diseases, such as metabolic brain diseases which includes phenylketonuria such as maternal phenylketonuria, pyruvate carboxylase deficiency, pyruvate dehydrogenase complex deficiency, Wernicke's Encephalopathy, brain edema, brain neoplasms such as cerebellar neoplasms which include infratentorial neoplasms, cerebral ventricle neoplasms such as choroid plexus neoplasms, hypothalamic neoplasms, supratentorial neoplasms, canavan disease, cerebellar diseases such as cerebellar ataxia which include spinocerebellar degeneration such as ataxia telangiectasia, cerebellar dyssynergia, Friederich's Ataxia, Machado-Joseph Disease, olivopontocerebellar atrophy, cerebellar neoplasms such as infratentorial neoplasms, diffuse cerebral sclerosis such as asencephalitis periaxialis, globoid cell leukodystrophy, metachromatic leukodystrophy and subacute sclerosing panencephalitis.

Additional neurologic diseases which can be treated or detected with modified fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention include cerebrovascular disorders (such as carotid artery diseases which include carotid artery thrombosis, carotid stenosis and Moyamoya Disease), cerebral amyloid angiopathy, cerebral aneurysm, cerebral anoxia, cerebral arteriosclerosis, cerebral arteriovenous malformations, cerebral artery diseases, cerebral embolism and thrombosis such as carotid artery thrombosis, sinus thrombosis and Wallenberg's Syndrome, cerebral hemorrhage such as epidermal hematoma, subdural hematoma and



subarachnoid hemorrhage, cerebral infarction, cerebral ischemia such as transient cerebral ischemia, Subclavian Steal Syndrome and vertebrobasilar insufficiency, vascular dementia such as multi-infarct dementia, periventricular leukomalacia, vascular headache such as cluster headache and migraine.

5 Additional neurologic diseases which can be treated or detected with modified fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention include dementia such as AIDS Dementia Complex, presenile dementia such as Alzheimer's Disease and Creutzfeldt-Jakob Syndrome, senile dementia such as Alzheimer's Disease and progressive supranuclear palsy, vascular dementia such as multi-infarct dementia, encephalitis which include encephalitis periaxialis, viral encephalitis such as epidemic encephalitis, Japanese Encephalitis, St. Louis Encephalitis, tick-borne encephalitis and West Nile Fever, acute disseminated encephalomyelitis, meningoencephalitis such as uveomeningoencephalitic syndrome, Postencephalitic Parkinson Disease and subacute sclerosing panencephalitis, encephalomalacia such as periventricular leukomalacia, epilepsy such as generalized epilepsy, which includes infantile spasms, absence epilepsy, myoclonic epilepsy which includes MERRF Syndrome, tonic-clonic epilepsy, partial epilepsy such as complex partial epilepsy, frontal lobe epilepsy and temporal lobe epilepsy, post-traumatic epilepsy, status epilepticus such as Epilepsia Partialis Continua, and Hallervorden-Spatz Syndrome.

20 Additional neurologic diseases which can be treated or detected with modified fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention include hydrocephalus such as Dandy-Walker Syndrome and normal pressure hydrocephalus, hypothalamic diseases such as hypothalamic neoplasms, cerebral malaria, narcolepsy which includes cataplexy, bulbar poliomyelitis, cerebri-pseudo tumor, Rett Syndrome, Reye's Syndrome, thalamic diseases, cerebral toxoplasmosis, intracranial tuberculoma and Zellweger Syndrome, central nervous system infections such as AIDS, Dementia Complex, Brain Abscess, subdural empyema, encephalomyelitis such as Equine Encephalomyelitis, Venezuelan Equine Encephalomyelitis, Necrotizing Hemorrhagic Encephalomyelitis, Visna, and cerebral malaria.

30 Additional neurologic diseases which can be treated or detected with modified fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention include meningitis such as arachnoiditis, aseptic meningitis such as viral meningitis which includes lymphocytic chronic meningitis, Bacterial meningitis which includes Haemophilus Meningitis, Listeria Meningitis, Meningococcal Meningitis

such as Waterhouse-Fridericisen Syndrome, Pneumococcal Meningitis and meningeal tuberculosis, fungal meningitis such as Cryptococcal Meningitis, subdural effusion, meniapencephalitis such as uvemenineroencephalitic syndrome, myelitis such as transverse myelitis, neurosyphilis such as tabes dorsalis, poliomyelitis which includes.

- 5 bulbar poliomyelitis and post poliomyelitis syndrome, prion diseases (such as Creutzfeldt-Jakob Syndrome, Bovine Spongiform Encephalopathy, Gerstmann-Straussler Syndrome, Kuru, Scrapie), and cerebral toxoplasmosis.

- Additional neurologic diseases which can be treated or detected with modified fusion proteins of the invention and/or polynucleotides encoding transferrin fusion
- 10 proteins of the invention include central nervous system neoplasms such as brain neoplasms that include cerebellar neoplasms such as infratentorial neoplasms, cerebral ventricle neoplasms such as choroidplexus neoplasms, hypothalamic neoplasms and supratentorial neoplasms, meningeal neoplasms, spinal cord neoplasms which include epidural neoplasms, demyelinating diseases such as Canavan Diseases, diffuse cerebral
- 15 sculleries which include sadrenoleukodystrophy, encephalitis periaxialis, globoid cell leukodystrophy, diffuse cerebral sclerosis such as metachromatic leukodystrophy, allergic encephalomyelitis, necrotizing hemorrhagic encephalomyelitis, progressive multifocal leukoencephalopathy, in multiple sclerosis, central pontine myelinolysis, transverse myelitis, neuroinflammation optica, Scrapie, Swayback, Chronic Fatigue Syndrome, Visna,
- 20 High Pressure Nervous Syndrome, Meningism, spinal cord diseases such as arriyotonia congenita, amyotrophic lateral-sclerosis, spinal muscular atrophy such as Werdnig-Hoffmann Disease, spinal cord compression, spinal cord neoplasms such as epidural neoplasms, syringomyelia., Tabes Dorsalis, Stiff-Man Syndrome, mental retardation such as Angelman Syndrome, Cri-du-Chat Syndrome, De Lange's Syndrome, Down Syndrome,
- 25 Gangliosidoses such as gangliosidoses G(MI), Sandhoff Disease, Tay-Sachs Disease, Hartnup Disease, homocystinuria, Laurence-Moon-Bied Syndrome, Lesch-Nylian Syndrome, Maple Syrup Urine Disease, mucopolysaccharidosis such as fucosidosis, neuronal ceroid-fipofuscinosis, oculocerebrorenal syndrome, phenylketonuria such as maternal phenylketonuria, Prader-Willi Syndrome, Rett Syndrome, Rubinstein-Taybi Syndrome,
- 30 Tuberous Sclerosis, WAGR Syndrome, nervous system abnormalities such as holoprosencephaly, neural tube defects such as anencephaly which includes hydrangencephaly, Arnold-Chairi Deformity, encephalocele, meningocele, meningomyelocele, spinal dysraphism such as Spina bifida cystica and spina bifida occulta.

Endocrine system and/or hormone imbalance and/or diseases encompass disorders of uterine motility including, but not limited to complications with pregnancy and labor (e.g., pre-term labor, post-term pregnancy, spontaneous abortion, and slow or stopped labor); and disorders and/or diseases of the menstrual cycle, (e.g., dysmenorrhea and  
5 endometriosis).

Endocrine system and/or hormone imbalance disorders and/or diseases include disorders and/or diseases of the pancreas, such as, for example, diabetes mellitus, diabetes insipidus, congenital pancreatic agenesis, pheochromocytoma islet cell tumor syndrome; disorders and/or diseases of the adrenal glands such as, for example, Addison's Disease,  
10 corticosteroid deficiency, virilizing disease, hirsutism, Cushing's Syndrome, hyperaldosteronism, pheochromocytoma; disorders and/or diseases of the pituitary gland, such as, for example, hyperpituitarism, hypopituitarism, pituitary dwarfism, pituitaryadenoma, panhypopituitarism, acromegaly, gigantism; disorders and/or diseases of the thyroid, including but not limited to, hyperthyroidism, hypothyroidism, Plummer's  
15 disease, Graves' disease (toxic diffuse goiter), toxic nodular goiter, thyroiditis (Hashimoto's thyroiditis, subacute granulomatous thyroiditis, and silent lymphocytic thyroiditis), Pendred's syndrome, myxedema, cretinism, thyrotoxicosis, thyroid hormone coupling defect, thymic aplasia, Hurthle cell tumors of the thyroid, thyroid cancer, thyroid carcinoma, Medullary thyroid carcinoma; disorders and/or diseases of the parathyroid,  
20 such as, for example, hyperparathyroidism, hypoparathyroidism; disorders and/or diseases of the hypothalamus.

In addition, endocrine system and/or hormone imbalance disorders and/or diseases may also include disorders and/or diseases of the testes or ovaries, including cancer. Other disorders and/or diseases of the testes or ovaries further include, for example,  
25 ovarian cancer, polycystic ovary syndrome, Klinefelter's syndrome, vanishing testes syndrome (bilateral anorchia), congenital absence of Leydig's cells, cryptorchidism, Noonan's syndrome, myotonic dystrophy, capillary haemangioma of the testis (benign), neoplasias of the testis and neotestis.

Moreover, endocrine system and/or hormone imbalance disorders and/or diseases  
30 may also include disorders and/or diseases such as, for example, polyglandular deficiency syndromes, pheochromocytoma, neuroblastoma, multiple Endocrine neoplasia, and disorders and/or cancers of endocrine tissues.

The modified transferrin fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention may be used for the diagnosis,

treatment, or prevention of diseases and/or disorders of the reproductive system.

Reproductive system disorders that can be treated by the compositions of the invention, include, but are not limited to, reproductive system injuries, infections, neoplastic disorders, congenital defects, and diseases or disorders will result in infertility,

5 complications with pregnancy, labor, or parturition, and postpartum difficulties.

Reproductive system disorders and/or diseases include diseases and/or disorders, of the testes, including testicular atrophy, testicular feminization, cryptorchism (unilateral and. bilateral), anorchia, ectopic testis, epididymitis and orchitis (typically resulting from infections such as, for example, gonorrhea, mumps, tuberculosis, and syphilis),

10 testicular torsion, vasitis nodosa, germ cell tumors (*e.g.*, seminomas, embryonal cell carcinomas, teratocarcinomas, choriocarcinomas, yolk sac tumors, and teratomas), stromal tumors (*e. g.*, Leydig cell tumors), hydrocele, hematocele, varicocele, spermatocele, inguinal hernia, and disorders of sperm production (*e. g.* immotile cilia syndrome, spermia, asthenozoospermia, azoospermia, oligospermia, and teratozoospermia).

15 Reproductive system disorders also include disorders of the prostate gland, such as acute non-bacterial prostatitis, chronic non-bacterial prostatitis, acute bacterial prostatitis, chronic bacterial prostatitis, postatodystonia, prostatosis, granulomatous prostatitis, malacoplakia, benign prostatic hypertrophy or hyperplasia, and prostate neoplastic disorders, including adenocarcinomas, transitional cell carcinomas, ductal carcinomas, and  
20 squamous cell carcinomas.

Additionally, the compositions of the invention may be useful in the diagnosis, treatment, and/or prevention of disorders or diseases of the penis and urethra, including inflammatory disorders, such as balanoposthitis, balanitis xerotica obliterans, phimosis, paraphimosis, syphilis, herpes simplex virus, gonorrhea, non-gonococcal urethritis,  
25 chlamydia, rhycoplasma, trichomonas, HIV, AIDS, Reiter's syndrome, condyloma acuminatum, condyloma latum, and pearly penile papules, urethral abnormalities, such as hypospadias, epispadias, and phimosis, premalignant lesions, including Erythroplasia of Queyrat, Bowen's disease, Bowenoid papulosis, criant condyloma of Buscke-Lowenstein, and verrucous carcinoma; penile cancers, including  
30 squamous cell carcinomas, carcinoma in situ, verrucous carcinoma, and disseminated penile carcinoma; urethral neoplastic disorders, including penile urethral carcinoma, bulbomembranous urethral carcinoma, and prostaticurethral carcinoma; and erectile disorders, such as priapism, Peyronie's disease, erectile dysfunction, and impotence.

Moreover, diseases and/or disorders of the vas deferens include vasculitis and CBAVD (congenital bilateral absence of the vas deferens); additionally, the transferrin fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention may be used in the diagnosis, treatment, and/or prevention of diseases and/or disorders of the seminal vesicles, including hydatid disease, congenital chloride diarrhea, and polycystic kidney disease.

Other disorders and/or diseases of the male reproductive system include, for example, Klinefelters syndrome, Young's syndrome, premature ejaculation, diabetes mellitus, cystic fibrosis, Kartagener's syndrome, high fever, multiple sclerosis, and gynecomastia.

Further, the polynucleotides, modified fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention may be used in the diagnosis treatment and/or prevention of diseases and/or disorders of the vagina and vulva, including bacterial vaginosis, candida vaginitis, herpes simplex virus, chancroid, granuloma inguinale, lymphogranuloma venereum, scabies, human papillomavirus, vaginal trauma, vulvar trauma, adenosis, chlamydia vaginitis, gonorrhea, trichomonas vaginitis, condyloma acuminatum, syphilis, molluscum contagiosum, atrophic vaginitis, Papanicolaou's disease, lichen sclerosus, lichen planus, vulvodynia, toxic shock syndrome, vaginismus, vulvovaginitis, vulvar vestibulitis, and neoplastic disorders, such as squamous cell hyperplasia, clear cell carcinoma, basal cell carcinoma, melanomas, cancer of Bartholin's gland, and vulvar intraepithelial neoplasia.

Disorders and/or diseases of the uterus include dysmenorrhea, retroverted uterus, endometriosis, fibroids, adenomyosis, anovulatory bleeding, amenorrhea, Cushner's syndrome, hydatidiform moles, Asherman's syndrome, premature menopause, precocious puberty, uterine polyps, dysfunctional uterine bleeding (*e.g.*, due to aberrant hormonal signals), and neoplastic disorders, such as adenocarcinomas, leiomyosarcomas, and sarcomas. Additionally, the transferrin fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention may be useful as a marker or detector of, as well as, in the diagnosis, treatment, and/or prevention of congenital uterine abnormalities, such as bicornuate uterus, septate uterus, simple unicornuate uterus, unicornuate uterus with a noncavitary rudimentary horn, unicornuate uterus with a non-communicating cavitary rudimentary horn, unicornuate uterus with a communicating cavitary horn, arcuate uterus, uterine didelphys, and T-shaped uterus.

Ovarian diseases and/or disorders include an ovulation, polycystic ovary syndrome (Stein-Leventhal syndrome), ovarian cysts, ovarian hypofunction, ovarian insensitivity to gonadotropins, ovarian over production of androgens, right ovarian vein syndrome, in amenorrhea, hirutism, and ovarian cancer (including, but not limited to, primary and  
5 secondary cancerous growth, Sertoli-Leydig tumors, endometriod carcinoma of the ovary, ovarian papillary serous adenocarcinoma, ovarian mucinous adenocarcinoma, and Ovarian Krukenberg tumors).

Cervical diseases and/or disorders include cervicitis, chronic cervicitis, mucopurulent cervicitis, and cervical. dysplasia, cervical polyps, Nabothian cysts, cervical  
10 erosion, cervical incompetence, and cervical neoplasms (including, for example, cervical carcinoma, squamous metaplasia, squamous cell carcinoma, adenosquamous cell neoplasia, and columnar cell neoplasia).

Modified transferrin fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention can be used to treat or detect  
15 infectious agents. For example, by increasing the immune response, particularly increasing the proliferation and differentiation of B and/or T cells, infectious diseases may be treated. The immune response may be increased by either enhancing an existing immune response, or by fusion proteins of the invention and/or initiating a new immune response. Alternatively, polynucleotides encoding transferrin fusion proteins of the  
20 invention may also directly inhibit infectious agent, without necessarily eliciting an immune response.

Viruses are one example of an infectious agent that can cause disease or symptoms that can be treated or detected by transferrin fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention. Examples of  
25 viruses, include, but are not limited to the following DNA and RNA viruses and viral families: Arbovirus, Adenoviridae, Arenaviridae, Arterivirus, Bimaviridae, Bunyaviridae, Caliciviridae, Circoviridae, Coronaviridae, Dengue, EBV, HIV, Flaviviridae, Hepadnaviridae Hepatitis, Herpesviridae (such as, Cytomegalovirus, Herpes Simplex, Berpes Zoster), Mononegavirus (*e.g.*, Paramyxoviridae, Morbillivirus, Rhabdoviridae),  
30 Orthomyxoviridae (*e.g.*, Influenza A, Influenza B, and parainfluenza), Papiloma virus, Papovaviridae, Parvoviridae, Picomaviridae, Poxviridae (such as Smallpox or Vaccinia), Reoviridae (*e. g.*, Rotavirus), Retroviridae (HTLV-I, HTLV-11, -Lentivirus), and Togaviridae (*e.g.*, Rubivirus).

Similarly, bacterial and fungal agents that can cause disease or symptoms that can be treated or detected by transferrin fusion proteins of the invention and/or

polynucleotides encoding transferrin fusion proteins of the invention include, but not

limited to, the following Gram-negative and Gram-positive bacteria, bacterial families,

5 and fungi: Actinomyces (e. g., Norcardia), Acinetobacter, Cryptococcus neoformans,

Aspergillus, Bacillaceae (e. g., Bacillus anthracis), Bacteroides (e.g., Bacteroides fragilis),

Blastomycosis, Bordetella, Borrelia (e.g., Borrelia burgdorferi), Brucella, Candida,

Campylobacter, Chlamydia, Clostridiaceae (e.g., Clostridium botulinum, Clostridium

difficile, Clostridium perfringens, Clostridium tetani), Coccidioides, Corynebacterium (e.g.,

10 Corynebacterium diphtheriae), Cryptococcus, Dermatocycoses, E. coli (e. g.,

Enterotoxigenic E. coli and Enterohemorrhagic E. coli), Enterobacter (e.g. Enterobacter

aerogenes), Enterobacteriaceae (Klebsiella, Salmonella (e.g., Salmonella typhi, Salmonella

enteritidis, Salmonella typhi), Serratia, Yersinia, Shigella), Erysipelothrix, Haemophilus

(e.g., Haemophilus influenza type B), Helicobacter, Legionella (e. g., Legionella

15 pneumophila), Leptospira, Listeria (e.g., Listeria monocytogenes), Mycoplasma,

Mycobacterium (e.g., Mycobacterium leprae and Mycobacterium tuberculosis), Vibrio

(e.g., Vibrio cholerae), Neisseriaceae (e.g., Neisseria meningitidis),

Pasteurellaceae, Proteus, Pseudomonas (e.g., Pseudomonas aeruginosa), Rickettsiaceae,

Spirochetes (e.g., Treponema spp., Leptospira spp., Borrelia spp.), Shigella spp.,

20 Staphylococcus (e.g., Staphylococcus aureus), Meningococcus, Pneumococcus and

Streptococcus (e.g., Streptococcus pneumoniae and Groups A, B, and C Streptococci), and

Ureaplasmas.

Moreover, parasitic agents causing disease or that can be treated, prevented, and/or diagnosed by fusion proteins of the invention and/or polynucleotides encoding transferrin

25 fusion proteins of the invention include, but not limited to, the following families or class:

Amebiasis, Babesiosis, Coccidiosis, Cryptosporidiosis, Dientamoebiasis, Dourine,

Ectoparasitic, Giardiasis, Helminthiasis, Leishmaniasis, Schistosoma, Theileriasis,

Toxoplasmosis, Trypanosomiasis, and Trichomonas and Sporozoans (e.g.,

Plasmodium vivax, Plasmodium falciparum, Plasmodium malariae and Plasmodium

30 ovale).

Modified transferrin fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention can be used to differentiate, proliferate, and attract cells, leading to the regeneration of tissues. (See, Science 276:59-87 (1997)). The regeneration of tissues could be used to repair, replace, or protect tissue

damaged by congenital defects, trauma (wounds, burns, incisions, or ulcers), age, disease (e.g. osteoporosis, osteoarthritis, periodontal disease, liver failure), surgery, including cosmetic plastic surgery, fibrosis, reperfusion injury, or systemic cytokine damage.

Tissues that could be regenerated using the present invention include organs (e.g., pancreas, liver, intestine, kidney, skin, endothelium), muscle (smooth, skeletal or cardiac), vasculature (including vascular and lymphatics), nervous, hematopoietic, and skeletal (bone, cartilage, tendon, and ligament) tissue. Preferably, regeneration occurs without or decreased scarring. Regeneration also may include angiogenesis.

Modified transferrin fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention, may be used to treat, prevent, diagnose, and/or prognose gastrointestinal disorders, including inflammatory diseases and/or conditions, infections, cancers (e.g., intestinal neoplasms (carcinoid tumor of the small intestine, non-Hodgkin's lymphoma of the small intestine, small bowel lymphoma), and ulcers, such as peptic ulcers.

Gastrointestinal disorders include dysphagia, odynophagia, inflammation of the esophagus, peptic esophagitis, gastric reflux, submucosal fibrosis and structuring, Mallory-Weiss lesions, leiomyomas, lipomas, epididymal cancers, adenocarcinomas, gastric retention disorders, gastroenteritis, gastric atrophy, gastric/stomach cancers, polyps of the stomach, autoimmune disorders such as pernicious anemia, pyloric stenosis, gastritis (bacterial, viral, eosinophilic, stress-induced, chronic erosive, atrophic, plasma cell, and Menetrier's), and peritoneal diseases (e.g., chylous peritoneum, hemoperitoneum, mesenteric cyst, mesenteric lymphadenitis, mesenteric vascular occlusion, panniculitis, neoplasms, peritonitis, pneumoperitoneum, subphrenic abscess.

Gastrointestinal disorders also include disorders associated with the small intestine, such as malabsorption syndrome's, distension, irritable bowel syndrome, sugar intolerance, celiac disease, duodenal ulcers, duodenitis, tropical sprue, Whipple's disease, intestinal lymphangiectasia, Crohn's disease, appendicitis, obstructions of the ileum, Meckel's diverticulum, multiple diverticula, failure of complete rotation of the small and large intestine, lymphoma, and bacterial and parasitic diseases (such as Traveler's diarrhea, typhoid and paratyphoid, cholera, infection by Roundworms (*Ascariasis tricomis*), Hookworms (*Anclostoma duodenale*), Threadworms (*Enterobius vermicularis*), Tapeworms *jaenia saginata*, *Echinococcus granulosus*, *Diphyllobothrium* spp. and *T. SOHUM*).



Liver diseases and/or disorders include intrahepatic cholestasis (alagille syndrome, biliary liver cirrhosis), fatty, liver (alcoholic fatty liver, reye syndrome), hepatic vein, thrombosis, hepatolenticular degeneration, hepatomegaly, hepatopulmonary syndrome, hepatorenal, syndrome, portal hypertension (esophageal and gastric varices), liver abscess  
 5 (amebic liver abscess), liver cirrhosis (alcoholic, biliary and experimental), alcoholic liver diseases (fatty liver, hepatitis, cirrhosis), parasitic (hepatic echinococcosis, fascioliasis, amebic liver abscess), jaundice (hemolytic, hepatocellular, and cholestatic), cholestasis, portal hypertension, liver, enlargement, ascites, hepatitis (alcoholic hepatitis, aniffial hepatitis, chronic hepatitis (autoimmune, hepatitis B, hepatitis C, hepatitis D, drug  
 10 induced), toxic hepatitis, viral human hepatitis (hepatitis A, hepatitis B, hepatitis C, hepatitis D, hepatitis E), Wilson's disease, granulomatous hepatitis, secondary biliary cirrhosis, hepaticencephalopathy, portal hypertension, varices, hepatic encephalopathy, primary biliary heinarigiomas, bilecirrhosis, primary sclerosing cholangitis, hepatocellular adenoma, stones, liver failure (hepatic encephalopathy, acute liver failure), and liver  
 15 neoplasins (ancrimiomyolipoma, calcified liver metastases, cystic liver metastases, epithelial tumors, fibro lamellar hepatocarcinoma, focal nodular hyperplasia, hepatic adenoma, hepatobiliarycystadenoma, hepatoblastoma, hepatocellular carcinoma, hepatoma, liver cancer, liver hemangioendothelioma, mesenchymal hamartoma, mesenchymal tumors of liver, nodular regenerative hyperplasia, benign liver tumors (Hepatic cysts, Simple cysts,  
 20 Polycystic liver disease, Hepatobiliary cystadenoma, Choledochal cysts, Mesenchymal tumors, Mesenchymal hamartoma, Infantile hemangioendothelioma, Hemangioma, Peliosis hepatis, Lipomas, Inflammatory pseudo tumor, Miscellaneous Epithelial tumors, Bile ductepitheflum (Bile duct hamartoma, Bile duct adenoma), Hepatocyte (Adenoma, Focal nodular hyperplasia, Nodular regenerative hyperplasia), malignant liver tumors  
 25 (hepatocellular, hepatoblastoma, hepatocellular carcinoma, cholangiocellular, cholangiocarcinoma, cystadenocarcinoma, tumors of blood vessels, anaiosa, Kaposi's sarcoma, hemangioendothelioma, other tumors, embryonal sarcoma, fibrosarcoma, leiomyosarcoma, rhabdomyosarcoma, carcinosarcoma, teratoma, carcinoid, squamous carcinoma, primarylymphoma)), peliosis hepatis, erythrohepatic porphyria,  
 30 hepatic porphyria (acute intermittent porphyria, porphyria cutanea tarda), Zellweger syndrome).

Pancreatic diseases and/or disorders include acute pancreatitis, chronic pancreatitis (acute necrotizing pancreatitis, alcoholic pancreatitis), neoplasins (adenocarcinoma of the pancreas, cystadenocarcinoma, insulinoma, gastrinoma, and glucagonoma,

cystic neoplasms, islet-cell tumors, pancreoblastoma), and other pancreatic diseases (e.g., cystic fibrosis, cyst (pancreatic pseudocyst, pancreatic fistula, insufficiency)).

Gallbladder diseases include gallstones (cholelithiasis and choledocholithiasis), postcholecystectomy syndrome, diverticulosis of the gallbladder, acute cholecystitis, chronic cholecystitis, bile duct tumors, and mucocele.

Diseases and/or disorders of the large intestine include antibiotic-associated colitis, diverticulitis, ulcerative colitis, acquired megacolon, abscesses, fungal and bacterial infections, anorectal disorders (e.g., fissures, hemorrhoids), colonic diseases (colitis, colonic neoplasms, colon cancer, adenomatous colon polyps (e.g., villous adenoma), colon carcinoma, colorectal cancer, colonic diverticulitis, colonic diverticulosis, megacolon, Hirschsprung disease, toxic megacolon, sigmoid diseases proctocolitis, sigmoid neoplasms, constipation, Crohn's disease, diarrhea (infantile diarrhea, dysentery), duodenal diseases (duodenal neoplasms, duodenal obstruction, duodenal ulcer, duodenitis), enteritis (enterocolitis), HIV enteropathy, ileal diseases (ileal neoplasms, ileitis), immunoproliferative small intestinal disease, inflammatory bowel disease (ulcerative colitis, Crohn's disease), intestinal atresia, parasitic diseases (anisakiasis, balantidiasis, blastocystis infections, cryptosporidiosis, dientamoebiasis, amebic dysentery, giardiasis), intestinal fistula (rectal fistula), intestinal neoplasms (cecal neoplasms, colonic neoplasms, duodenal neoplasms, ileal neoplasms, intestinal polyps, jejunal neoplasms, rectal neoplasms), intestinal obstruction (afferent loop syndrome, duodenal obstruction, impacted feces, intestinal pseudo obstruction cecal volvulus, intussusception), intestinal perforation, intestinal polyps (colonic polyps, gardner syndrome, peutz-jeghers syndrome), jejunal diseases (jejunal neoplasms), malabsorption syndromes (blind loop syndrome, celiac disease, lactose intolerance, short bowel syndrome, tropical sprue, whipple's disease), mesenteric vascular occlusion, pneumatosis cystoides intestinalis, protein losing enteropathies (intestinal lymphangiectasis), rectal diseases (anus diseases, fecal incontinence, hemorrhoids, proctitis, rectal fistula, rectal prolapse, rectocele), peptic ulcer (duodenal ulcer, peptic esophagitis, hemorrhage, perforation, stomach ulcer, Zollinger-Ellison syndrome), postgastrectomy syndromes (dumping syndrome), stomach diseases (e.g., achlorhydria, duodenogastric reflux (bile reflux), gastric antral vascular ectasia, gastric fistula, gastric outlet obstruction, gastritis (atrophic or hypertrophic), gastroparesis, stomach dilatation, stomach diverticulum, stomach neoplasms (gastric cancer, gastric polyps, gastric adenocarcinoma, hyperplastic gastric polyp), stomach rupture, stomach ulcer, stomach volvulus), tuberculosis, viscerotaxis,

vomiting (*e.g.*, hematemesis, hyperemesis gravidarum, postoperative nausea-and vomiting) and hemorrhagic colitis.

Further diseases and/or disorders of the gastrointestinal system include biliary tract diseases, such as, gastroschisis, fistula (*e.g.*, biliary fistula, esophageal fistula, gastric fistula, intestinal fistula, pancreatic fistula), neoplasms (*e.g.*, biliary tract neoplasms, esophageal neoplasms, such as adenocarcinoma of the esophagus, esophageal squamous cell carcinoma, gastrointestinal neoplasms, pancreatic neoplasms, such as adenocarcinoma of the pancreas, mucinous cystic neoplasm of the pancreas, pancreatic cystic neoplasms, pancreatoblastoma, and peritoneal neoplasms), esophageal disease (*e.g.*, bullous diseases, candidiasis, glycoacanthosis, ulceration, Barrett esophagus varices, atresia, cyst, diverticulum. (*e.g.*, Zenker's diverticulum), fistula (*e.g.*, tracheoesophageal fistula), motility disorders (*e.g.*, CREST syndrome, deglutition disorders, achalasia, spasm, gastroesophageal reflux), neoplasms, perforation (*e.g.*, Boerhaave syndrome, Mallory-Weiss syndrome), stenosis, esophagitis, diaphragmatic hernia (*e.g.*, hiatal hernia); gastrointestinal diseases, such as, gastroenteritis (*e.g.*, cholera morbus, norwalk virus infection), hemorrhage (*e.g.*, hematemesis, melena, peptic ulcer hemorrhage), stomach neoplasms (gastric cancer, gastric polyps, gastric adenocarcinoma, stomach cancer)), hernia (*e.g.*, congenital diaphragmatic hernia, femoral hernia, inguinal hernia, obturator hernia, umbilical hernia, ventral hernia), and intestinal diseases (*e.g.*, cecal diseases (appendicitis, cecal neoplasms)).

Modified transferrin fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention may have chemotaxis activity. A chemotactic molecule attracts or mobilizes cells (*e.g.*, monocytes, fibroblasts, neutrophils, T-cells, mast cells, eosinophils, epithelial and/or endothelial cells) to a particular site in the body, such as inflammation, infection, or site of hyperproliferation. The mobilized cells can then fight off and/or heal the particular trauma or abnormality.

Modified transferrin fusion proteins of the invention and/or polynucleotides encoding transferrin fusion proteins of the invention may increase chemotactic activity of particular cells. These chemotactic molecules can then be used to treat inflammation, infection, hyperproliferative disorders, or any immune system disorder by increasing the number of cells targeted to a particular location in the body.

### Transgenic Animals

The production of transgenic non-human animals that contain a modified transferrin fusion construct with increased serum half-life increased serum stability or increased bioavailability of the instant invention is contemplated in one embodiment of the present invention. In some embodiments, lactoferrin may be used as the Tf portion of the fusion protein so that the fusion protein is produced and secreted in milk.

The successful production of transgenic, non-human animals has been described in a number of patents and publications, such as, for example U.S. Patent 6,291,740 (issued September 18, 2001); U.S. Patent 6,281,408 (issued August 28, 2001); and U.S. Patent 6,271,436 (issued August 7, 2001) the contents of which are hereby incorporated by reference in their entireties.

The ability to alter the genetic make-up of animals, such as domesticated mammals including cows, pigs, goats, horses, cattle, and sheep, allows a number of commercial applications. These applications include the production of animals which express large quantities of exogenous proteins in an easily harvested form (*e.g.*, expression into the milk or blood), the production of animals with increased weight gain, feed efficiency, carcass composition, milk production or content, disease resistance and resistance to infection by specific microorganisms and the production of animals having enhanced growth rates or reproductive performance. Animals which contain exogenous DNA sequences in their genome are referred to as transgenic animals.

The most widely used method for the production of transgenic animals is the microinjection of DNA into the pronuclei of fertilized embryos (Wall *et al.*, J. Cell. Biochem. 49:113 [1992]). Other methods for the production of transgenic animals include the infection of embryos with retroviruses or with retroviral vectors. Infection of both pre- and post-implantation mouse embryos with either wild-type or recombinant retroviruses has been reported (Janenich, Proc. Natl. Acad. Sci. USA 73:1260 [1976]; Janenich *et al.*, Cell 24:519 [1981]; Stuhlmann *et al.*, Proc. Natl. Acad. Sci. USA 81:7151 [1984]; Jahner *et al.*, Proc. Natl. Acad. Sci. USA 82:6927 [1985]; Van der Putten *et al.*, Proc. Natl. Acad. Sci. USA 82:6148-6152 [1985]; Stewart *et al.*, EMBO J. 6:383-388 [1987]).

An alternative means for infecting embryos with retroviruses is the injection of virus or virus-producing cells into the blastocoele of mouse embryos (Jahner, D. *et al.*, Nature 298:623 [1982]). The introduction of transgenes into the germline of mice has been reported using intrauterine retroviral infection of the midgestation mouse embryo (Jahner *et al.*, supra [1982]). Infection of bovine and ovine embryos with retroviruses or retroviral vectors to create transgenic animals has been reported. These protocols involve the micro-

injection of retroviral particles or growth arrested (*i.e.*, mitomycin C-treated) cells which shed retroviral particles into the perivitelline space of fertilized eggs or early embryos (PCT International Application WO 90/08832 [1990]; and Haskell and Bowen, *Mol. Reprod. Dev.*, 40:386 [1995]. PCT International Application WO 90/08832 describes the injection of wild-type feline leukemia virus B into the perivitelline space of sheep embryos at the 2 to 8 cell stage. Fetuses derived from injected embryos were shown to contain multiple sites of integration.

U.S. Patent 6,291,740 (issued September 18, 2001) describes the production of transgenic animals by the introduction of exogenous DNA into pre-maturation oocytes and mature, unfertilized oocytes (*i.e.*, pre-fertilization oocytes) using retroviral vectors which transduce dividing cells (*e.g.*, vectors derived from murine leukemia virus [MLV]). This patent also describes methods and compositions for cytomegalovirus promoter-driven, as well as mouse mammary tumor LTR expression of various recombinant proteins.

U.S. Patent 6,281,408 (issued August 28, 2001) describes methods for producing transgenic animals using embryonic stem cells. Briefly, the embryonic stem cells are used in a mixed cell co-culture with a morula to generate transgenic animals. Foreign genetic material is introduced into the embryonic stem cells prior to co-culturing by, for example, electroporation, microinjection or retroviral delivery. ES cells transfected in this manner are selected for integrations of the gene via a selection marker such as neomycin.

U.S. Patent 6,271,436 (issued August 7, 2001) describes the production of transgenic animals using methods including isolation of primordial germ cells, culturing these cells to produce primordial germ cell-derived cell lines, transforming both the primordial germ cells and the cultured cell lines, and using these transformed cells and cell lines to generate transgenic animals. The efficiency at which transgenic animals are generated is greatly increased, thereby allowing the use of homologous recombination in producing transgenic non-rodent animal species.

### Gene Therapy

The use of modified transferrin fusion constructs for gene therapy wherein a modified transferrin protein or transferrin domain is joined to a therapeutic protein or peptide is contemplated in one embodiment of this invention. The modified transferrin fusion constructs with increased serum half-life or serum stability of the instant invention are ideally suited to gene therapy treatments.

The successful use of gene therapy to express a soluble fusion protein has been described. Briefly, gene therapy via injection of an adenovirus vector containing a gene encoding a soluble fusion protein consisting of cytotoxic lymphocyte antigen 4 (CTLA4) and the Fc portion of human immunoglobulin G1 was recently shown in Ijima *et al.* (June 5 10, 2001) Human Gene Therapy (United States) 12/9:1063-77. In this application of gene therapy, a murine model of type II collagen-induced arthritis was successfully treated via intraarticular injection of the vector.

Gene therapy is also described in a number of U.S. patents including U.S. Pat. 6,225,290 (issued May 1, 2001); U.S. Pat. 6,187,305 ( issued February 13, 2001); and U.S. 10 Pat. 6,140,111 (issued October 31, 2000).

U.S. Patent 6,225,290 provides methods and constructs whereby intestinal epithelial cells of a mammalian subject are genetically altered to operatively incorporate a gene which expresses a protein which has a desired therapeutic effect. Intestinal cell transformation is accomplished by administration of a formulation composed primarily of 15 naked DNA, and the DNA may be administered orally. Oral or other intragastrintestinal routes of administration provide a simple method of administration, while the use of naked nucleic acid avoids the complications associated with use of viral vectors to accomplish gene therapy. The expressed protein is secreted directly into the gastrointestinal tract and/or blood stream to obtain therapeutic blood levels of the protein thereby treating the 20 patient in need of the protein. The transformed intestinal epithelial cells provide short or long term therapeutic cures for diseases associated with a deficiency in a particular protein or which are amenable to treatment by overexpression of a protein.

U.S. Pat. 6,187,305 provides methods of gene or DNA targeting in cells of vertebrate, particularly mammalian, origin. Briefly, DNA is introduced into primary or 25 secondary cells of vertebrate origin through homologous recombination or targeting of the DNA, which is introduced into genomic DNA of the primary or secondary cells at a preselected site.

U.S. Pat. 6,140,111 (issued October 31, 2000) describes retroviral gene therapy vectors. The disclosed retroviral vectors include an insertion site for genes of interest and are capable of expressing high levels of the protein derived from the genes of interest in a 30 wide variety of transfected cell types. Also disclosed are retroviral vectors lacking a selectable marker, thus rendering them suitable for human gene therapy in the treatment of a variety of disease states without the co-expression of a marker product, such as an antibiotic. These retroviral vectors are especially suited for use in certain packaging cell

lines. The ability of retroviral vectors to insert into the genome of mammalian cells have made them particularly promising candidates for use in the genetic therapy of genetic diseases in humans and animals. Genetic therapy typically involves (1) adding new genetic material to patient cells *in vivo*, or (2) removing patient cells from the body, adding new  
5 genetic material to the cells and reintroducing them into the body, *i.e.*, *in vitro* gene therapy. Discussions of how to perform gene therapy in a variety of cells using retroviral vectors can be found, for example, in U.S. Pat. Nos. 4,868,116, issued Sep. 19, 1989, and 4,980,286, issued Dec. 25, 1990 (epithelial cells), WO89/07136 published Aug. 10, 1989 (hepatocyte cells) , EP 378,576 published Jul. 25, 1990 (fibroblast cells), and  
10 WO89/05345 published Jun. 15, 1989 and WO/90/06997, published Jun. 28, 1990 (endothelial cells), the disclosures of which are incorporated herein by reference.

Without further description, it is believed that a person of ordinary skill in the art can, using the preceding description and the following illustrative examples, make and  
15 utilize the present invention and practice the claimed methods. For example, a skilled artisan would readily be able to determine the biological activity, both *in vitro* and *in vivo*, for the fusion protein constructs of the present invention as compared with the comparable activity of the therapeutic moiety in its unfused state. Similarly, a person skilled in the art could readily determine the serum half life and serum stability of constructs according to  
20 the present invention. The following working examples therefore, specifically point out the preferred embodiments of the present invention, and are not to be construed as limiting in any way the remainder of the disclosure.

**EXAMPLES*****Example 1***

A fusion protein between modified Tf and an antifusogenic HIV-1 peptide (T-20) comprising the sequence is made by fusing one or more copies of the nucleotide sequence encoding the peptide to the nucleotide sequence of TF to produce a fusion protein with a peptide fused to the N- or C-terminus of Tf.

In one embodiment, the Tf portion of the fusion protein is engineered to not allow glycosylation when produced in yeast. As discussed above, human transferrin has two N-linked glycosylation sites at about N413 and about N611. The N-linked glycosylation site comprises the sequence N-X-S/T. In one embodiment, N (Asn) is changed to Q (Gln); other changes are contemplated such as Asn to Ala or Ser or any other amino acid.

Specifically, the N413 and N611 codons are converted to GAT and GAC by oligonucleotide directed mutagenesis using the dut- and ung-method. See Kunkel *et al.* (1985) *Proc. Natl. Acad. Sci.* 82:488-492). The mutagenic oligonucleotides 5'-GCAGAAACTACGATAAGAGCGATAAT-3' (SEQ ID NO: 9) and 5'-CTATTTGGAAGCGACGTAAGTACTGCTGC-3' (SEQ ID NO: 10) are synthesized and used to mutagenize the N413 and N611 codons according to the methods of Funk *et al.* (U.S. Patent 5,986,067).

Receptor binding and/or iron or carbonate binding is then disrupted by mutating the following iron and/or carbonate ion binding residues:

**Iron binding****N domain**

Asp 63 (Asp 82 of SEQ ID NO: 2)  
Tyr 95 (Tyr 114 of SEQ ID NO: 2)  
Tyr 188 (Tyr 207 of SEQ ID NO: 2)  
His 249 (His 268 of SEQ ID NO: 2)

**C domain**

Asp 392 (Asp 411 of SEQ ID NO: 2)  
Tyr 426 (Tyr 445 of SEQ ID NO: 2)  
Tyr 514 or 517 (Tyr 533 or Tyr 536 SEQ ID NO: 2)  
His 585 (His 604 of SEQ ID NO: 2)

**Carbonate ion binding****N domain**

Thr 120 (Thr 139 of SEQ ID NO: 2)  
Arg 124 (Arg 143 of SEQ ID NO: 2)  
Ala 126 (Ala 145 of SEQ ID NO: 2)  
Gly 127 (Gly 146 of SEQ ID NO: 2)

**C domain**

Thr 452 (Thr 471 of SEQ ID NO: 2)  
Arg 456 (Arg 475 of SEQ ID NO: 2)  
Ala 458 (Ala 477 of SEQ ID NO: 2)  
Gly 459 (Gly 478 of SEQ ID NO: 2)

The production of mutants deficient in iron binding may be accomplished by numerous techniques. See U.S. Patent 5,986,067. A D63S substitution may be prepared using the method of Nelson, R. M. and Long, G. L. (1989) *Analyt. Biochem.* 180:147-151. Briefly, a HpaII/BamHI fragment from the 5' end of the hTF/2N coding sequence is



subcloned into pUC18 and then used as a template for a two step PCR-based mutagenesis procedure. The fragment is then released from the double stranded form of the sequencing vector by digestion with XbaI and BamHI and then ligated to a BamHI/HindIII fragment from the original human Tf construct to produce a full length D63S-coding sequence, the fidelity of this splicing is confirmed by restriction digestion analysis.

For expression in *Pichia* the system from RCT/Invitrogen can be used. Three vectors are available for multicopy expression, pPIC9K, pPIC3.5K and pAO815. For this example the pPIC9K vector, which allows secretion into the growth medium, is used.

The modified transferrin sequence was cloned into the pPIC9K vector by altering the ends of the transferrin cDNA by overlapping PCR mutagenesis, this yielded the vector pREX0010. A number of restriction sites within the vector and coding sequence were removed or added to aid later cloning steps (Figure 5).

The sequence for the HIV anti-fusogenic peptide DP-178 is also known as T-20. This peptide lends itself to fusion at the N- or C- termini of Transferrin, as the peptide may need freedom of movement to fulfill its function.

DP-178 sequence: YTSLIHSLIEESQNQQEKNEQELLELDKWASLWNWF (SEQ ID NO: 4)

When back translated in to DNA (using codons optimized for yeast) the following sequence was obtained (SEQ ID NOS: 13 and 14):

```
tacacaagcttaatacactccttaattgaagaatcgcaaaaccagcaagaaaagaatgaacaagaatta
y t s l i h s l i e e s q n q q e k n e q e l
ttggaattagataaatgggcaagtttggtgaattggttt
l e l d k w a s l w n w f
```

To inset the above sequence the vector pREX0010 with the modified transferrin cDNA, was digested with the restriction enzymes *Xba* I/*Kpn* I for insertion at the 5' end and *Sal* I/*Hind* III for insertion at the 3' end.

For the 5' insertion two overlapping oligos that form an *Xba* I overhang at the 5' end and a *Kpn* I overhang at the 3' end of the DP-178 sequence given above were synthesized. These oligos were then annealed together (see below) and ligated into the *Xba* I/ *Kpn* I digested pREX0010 vector.

```

XbaI
-----
1  ctagagaaaa ggtacactag cttaatcac tccttaattg aagaatcgca aaaccagcaa gaaaagaatg aacaagaatt
5  tctttt ccatgtgato gaattatgtg aggaattaac ttcttagcgt ttgggtcgtt cttttcttac ttgttcttaa
   1 e k r y t s l i h s l i e e s q n q q e k n e q e
   >>.....T-20.....>
   >>.....>>

KpnI
-----
10 81 attggaatta gataaatggg caagtttgtg gaattggttt gtac
   taaccttaat ctatttacct gttcaaacac cttaaccaaa
   1 l e l d k w a s l w n w f v
   >>>>
   >.....T-20.....>>
15

```

SEQ ID NOS: 15 and 16

Insertion of the annealed oligos resulted in loss of the *Kpn* I site upon insertion. This resulted in the vector pREX0011 (Figure 6).

For insertion at the C-terminus a similar approach was taken by the addition of a *Sal*I site at the 5' end and a *Hind*III at the 3' end (Figure 7).

Transformation, selection and expression are then performed as described in the Invitrogen *Pichia* Expression kit protocol booklet.

### Example 2

INGAP fusions are prepared using a reverse translated human INGAP amino acid sequence. The protein sequence is as follows: sp|Q92778|PBCG\_HUMAN Human INGAP

```

MMLPMTLCRMSWMLLSCLMFLSWVEGEESQKKLPSSRITCPQGSVAYGSYCYSL
ILIPQTWSNAELSCQMHFSGHLAFLSTGEITFVSSLVKNSLTAYQYIW[IGLHDP
30 GTLPNG]GWKWSSSNVLTfYNWERNPSIAADRGYCAVLSQKSGFQKWRDFNCEN
ELPYICKFKV (SEQ ID NO: 17)

```

Reverse translated in to DNA (codons optimized for yeast) gave the following (SEQ ID NO: 18 and 19).

```

5      1  atgatgttgc caatgacttt gtgtagaatg tcttggatgt tgttgtottg tttgatgttt
      m m l p m t l c r m s w m l l s c l m f
      61  ttgtcttggg ttgaagggtga agaattctcaa aaaaaattgc catcttctag aattacttgt
10      l s w v e q e e s q k k l p s s r i t c
      121  ccacaagggt ctgttgetta tggttcttat tgttattctt tgattttgat tccacaaact
      p q g s v a y g s y c y s l i l i p q t
15      181  tgggtctaag ctgaattgtc ttgtcaaatg catttttctg gtcatttggc ttttttgttg
      w s n a e l s c q m h f s g h l a f l l
      241  tctactggtg aaattacttt tgtttcttct ttgggttaaaa attctttgac tgcttatcaa
      s t g e i t f v s s l v k n s l t a y q
20      301  tat [atttggga ttggtttgca tgatccatct catggtactt tgccaaatgg ttct] ggttgg
      y i w i g l h d p s h g t l p n g s g w
      361  aaatggtctt cttctaagt tttgactttt tataattggg aaagaaatcc atctattgct
25      k w s s s n v l t f y n w e r n p s i a
      421  gctgatagag gttattgtgc tgttttgtct caaaaatctg gttttcaaaa atggagagat
      a d r g y c a v l s q k s g f q k w r d
30      481  ttttaattgtg aaaatgaatt gccatatatt tgtaaattta aagtt
      f n c e n e l p y i c k f k v

```

The most likely point for cleavage of the leader sequence is at the KK at the end of the underlined sequence above.

One methodology which may be used to generate constructs for the expression of  
 35 INGAP fused to the N- or C-terminus of transferrin is to synthesize a series of overlapping oligos designed from the sequence given above (minus the underlined leader sequence). Annealing of these primers generates the INGAP cDNA. With different oligos designed for the 5' and 3' ends the annealed cDNA can be ligated into pREX0010 at the 5' or 3' end of Transferrin.

40 The bracketed sequence is the peptide used to induce INGAP activity. Hence the sequence could be paired down to some point between the whole and this minimal sequence.

**N-terminal fusion.**

For the N-terminus these would have an overhang which forms an *Xba*I site at the 5' end and an overhang compatible with a *Kpn*I site at the 3' end but which results in the

5 destruction of the *Kpn*I site.

```

      XbaI
      ---
10  1  ctagagaaaa ggttgccatc ttccagaatt acttgccac aaggttctgt tgcttatggt
      tctttt ccaacggtag aaggctcttaa tgaacagggtg ttccaagaca acgaatacca
      l e k   r l p   s s r i   t c p   q g s   v a y g

61  tcttattggt attctttgat ttgattcca caaacttggt ctaatgctga attgtcttgt
15  agaataacaa taagaaacta aaactaagggt gtttgaacca gattacgact taacagaaca
      s y c   y s l   i l i p   q t w   s n a   e l s c

121 caaatgcatt tttctgggtca ttgggtcttt ttgttgtcta ctggtgaaat tacttttgggt
20  gtttacgtaa aaagaccagt aaaccgaaaa aacaacagat gaccacttta atgaaaacaa
      q m h   f s g   h l a f   l l s   t g e   i t f v

181 tcttcttttg ttaaaaattc ttgactgct tatcaatata ttgggattgg ttgcatgat
      agaagaaacc aatttttaag aaactgacga atagttatat aaacctaac aaacgtacta
      s s l   v k n   s l t a   y q y   i w i   g l h d

25  241 ccatctcatg gtactttgcc aaatgggtct ggttggaat ggtcttcttc taatgttttg
      ggtagagtac catgaaacgg tttagcaga ccaaccttta ccagaagaag attacaaaac
      p s h   g t l   p n g s   g w k   w s s   s n v l

30  301 actttttaca attgggaaag aaatccatct attgctgctg atagaggtta ttgtgctggt
      tgaaaaatgt taaccttttc tttaggtaga taacgacgac tatctccaat aacacgacaa
      t f y   n w e   r n p s   i a a   d r g   y c a v

361 ttgtctcaaa aatctggttt tcaaaaatgg agagatttta attgtgaaaa tgaattgcca
35  aacagagttt ttagaccaa agtttttacc tctctaaaat taacactttt acttaacgggt
      l s q   k s g   f q k w   r d f   n c e   n e l p

      KpnI
      ----
40  421 tatatttgta aatttaaagt tgtac
      atataaacat ttaaatttca a
      y i c   k f k   v v

```

SEQ ID NOS: 20 and 21

Digestion of pREX0010 with *Xba*I and *Kpn*I and ligation of the above sequence yields the vector pREX0013 (Figure 8).

**C-terminal fusion.**

For the C-terminus the 5' end would form a *SaII* site and at the 3' end a stop codon plus a *HindIII* site.

5

*SaII*  
---

10

1 tgcacctttg ccactcttcca gaattacttg tccacaagggt tctggtgctt atggttctta  
ggaaac ggtagaagggt cttaatgaac aggtggtcca agacaacgaa taccaagaat  
r p l p s s r i t c p q g s v a y g s

15

61 ttgttattct ttgattttga ttccacaaac ttggtctaata gctgaattgt cttgtcaaata  
aacaataaga aactaaaact aagggtgtttg aaccagatta cgacttaaca gaacagttta  
y c y s l i l i p q t w s n a e l s c q

20

121 gcatttttct ggctcatttg cttttttgtt gtctactgggt gaaattactt ttgtttcttc  
cgtaaaaaga ccagtaaacg gaaaaaacia cagatgacca ctttaatagaa aacaaagaag  
m h f s g h l a f l l s t g e i t f v s

25

181 tttgggtaaa aattctttga ctgcttatca atatatattgg attgggttgc atgatccatc  
aaaccaattt ttaagaaact gacgaatagt tatataaacg taaccaaacy tactaggtag  
s l v k n s l t a y q y i w i g l h d p

30

241 tcatgggtact ttgccaaatg gttctgggtg gaaatgggtct tcttctaatag ttttgacttt  
agtaccatga aacgggtttac caagaccaac ctttaccaga agaagattac aaaactgaaa  
s h g t l p n g s g w k w s s s n v l t

35

301 ttacaattgg gaaagaaatc catctattgc tgctgataga gggtattgtg ctgttttctc  
aatgttaacc ctttcttttag gtatataacg acgactatct ccaataaacac gacaaaacag  
f y n w e r n p s i a a d r g y c a v l

361 tcaaaaatct gggttttcaa aatggagaga ttttaattgt gaaaatgaat tgccatatat  
agttttttaga ccaaaagttt ttacctctct aaaattaaca cttttactta acggtatata  
s q k s g f q k w r d f n c e n e l p y

*HindIII*

40

421 ttgtaaattt aaagttaa a  
aacattttaa tttcaaatta ttgga  
i c k f k v -

SEQ ID NOS 22 and 23

Digestion of pREX0010 with *SaII* and *HindIII* and ligation of the above sequence yields the vector pREX0014 (Figure 9).

Transformation, selection and expression are then performed as described in the Invitrogen *Pichia* Expression kit protocol booklet.

**Example 3**

The peptide given below has been shown to mimic EPO activity by causing dimerisation of the EPO receptor. The peptide, which is cyclic, has no homology to EPO. For activity the peptide has to act in concert with another peptide, *i.e.* as a dimer, such that two copies of the receptor are brought in close enough proximity to form an active complex. As with many peptides the peptide dimer suffers from short half life and would benefit from the longevity that fusion to transferrin would give. In this example two peptides are engineered into the transferrin scaffold.

10     1   ggtggtactt actcttgtca ttttgggtcca ttgacttggg tttgtaagcc acaaggtggt  
           g g t y s c h f g p l t w v c k p q g g

SEQ ID NOS: 24 and 25.

As detailed by Ali *et al*, a peptide can be successfully engineered into Transferrin between His289 and Gly290. The duplication inherent to the transferrin molecule, with the two domains mirroring each other, means that it is possible to engineer a peptide into the duplicate region of the C domain, between Glu625 and Thr626.

20            N   277   D-KSKE--FQ LFSSPHGKDL LFKDSAHGFL KVPPRMDAKM YLGYEYVTAI  
               C   611   NVTDCSGNFC LFRSETKDL LFRDDTVCLA KLHDRNTYEK YLGEEYVKAV

SEQ ID NOS: 26 and 27.

For each insertion two overlapping mutagenic primers are synthesized (see below). Using pREX0010 as a template reactions were performed with each mutagenic primer and an external primer from the 5' or 3' of the Tf cDNA. The products from these two reactions were then mixed and a further reaction performed with the external primers to join the two products together. The His289-Gly290 insert PCR product was digested with *Xba*I and *Hpa*I for ligation into *Xba*I/*Hpa*I digested pREX0010. The resulting vector was then digested with *Hpa*I and *Sal*I for ligation of *Hpa*I/*Sal*I digested the Glu625-Thr626 insert PCR product.

## His289-Gly290 insert (SEQ ID NO: 28).

```

5      2031  agacaaatca[aaagaatttc aactattcag ctctctcat ggtggtactt actcttgtoa ttttggtcca
      tctgttttagt tttcttaaag ttgataagtc gagaggagta ccaccatgaa[tgagaacagt aaaaccaggt
      >>.....EMOm.....>
      >.....Tf.....>
      >.....N domain.....>
10     2101  ttgacttggg tttgtaagcc]acaagggtggt gggaaggacc tgctgtttta ggactctgcc cacgggtttt
      aactgaaccc aacatttcgg tgttccacca ccttctctgg acgacaaatt cctgagacgg]gtgccccaaa
      ----->
      >.....EMOm.....>>
      >.....Tf.....>
      >.....N domain.....>
15

```

## Glu625-Thr626 insert (SEQ ID NO: 29).

```

20     3081  cctatttga agcaacgtaa ctgactgctc[gggcaacttt tgttgtttcc ggtcggaagg tggtaactac
      ggataaacct tcgttgcat gactgacgag cccgttgaaa acaaacagg ccagccttcc accatgaat[g
      >>...EPom...>
      >.....C domain.....>
      >.....Tf.....>
25
      KpnI
      -----
30     3151  tcttgtcatt ttggtccatt gacttgggtt tgtaagccac]aagggtggtac caaggacctt ctgttcagag
      agaacagtaa aaccaggtaa ctgaacccaa acattcgggtg ttccaccatg gttcctggaa gacaagtctc
      ----->
      >.....EPom.....>>
      >.....C domain.....>
      >.....Tf.....>
35     3221  atgacacagt atgtttggcc aaacttcatt acagaaacac atatgaaaaa tacttaggag aagaatatgt
      tactgtgtca]tacaacccgg tttgaagtac tgtctttgtg tatacttttt atgaatcctc ttcttataca
      >.....C domain.....>
      >.....Tf.....>

```

These gave the plasmid pREX0015 (Figure 10). Transformation, selection and  
 40 expression are then performed as described in the Invitrogen *Pichia* Expression kit  
 protocol booklet.

Alternative points for insertion of the EPO mimetic peptide(s), or any other  
 peptide(s) are the two glycosylation sites on the C domain of Transferrin at N413 and  
 N611. The advantage of this would be that insertion is achieved and glycosylation  
 45 prevented, by disruption of the N-X-S/T sequence, in one and the same event.

**Example 4**

Fusion proteins between Tf and fusogenic inhibitor peptides against RSV are made by fusing the peptide sequences to the N- or C- terminal ends of Tf or by the insertion of the sequences into a loop of Tf, wherein the Tf is modified to not bind iron and/or is modified to prevent glycosylation. The RSV peptide may include: T786:

VYPSDEYDASISQVNEEINQALAYIRKADELLENV (SEQ ID NO: 5) and/or T1584:  
AVSKVLHLEGEVKNKIKSALLSTNKAVVSLSNGVSVLTSKVLDLKNYIDKQL (SEQ ID NO: 6).

The T786 peptide has a RK dipeptide which could act as a cleavage site for the yeast protease Kex2p. This would result in a truncated peptide. Accordingly, this peptide may be modified from RK to RE. Another version of the T786 peptide, T112 (VFPSDEFDASISQVNEKINQSLAFIRESDELLHNV, SEQ ID NO: 7), which is more potent than T786 has solubility problems in its unfused form. Accordingly, a version of T112 modified for the RK to RE is also made to produce a version of the peptide fused to Tf.

To produce the genetic constructs, the peptide sequences are backtranslated in DNA using codon bias for human, yeast or any other organism as appropriate.

**Example 5**

Various cytokines can be fused to the N-, C- or N- and C- termini of Tf. These fusions can also be constructed using different parts or domains of modified transferrin such as the N domain or C domain. The proteins can be fused directly or using a linker peptide of various lengths. It is also possible to fuse all or part of the active cytokine within the scaffold of transferrin.

The cDNA for the cytokine of interest, such as EPO, can be isolated by a variety of means such as RT-PCR from mRNA, from cDNA libraries, by synthetically constructing the cDNA from overlapping oligonucleotides, by PCR or by other means known to the art, all using standard methods. The nucleotide sequences for all of these proteins are known and available, for instance, in U.S. Patents 4,703,008, 4,810,643 and 5,908,763 as well as in public databases such as GenBank. The cDNA can be tailored at the 5' and 3' ends to generate restriction sites, such that oligonucleotide linkers can be used, for cloning of the cDNA into a vector containing the cDNA for Transferrin. This can be at the N- or C-terminus, with or without the use of a spacer sequence, or by inserting the cDNA of the cytokine within the cDNA of Transferrin. The cytokine, *e.g.* EPO, and Tf cDNA are



cloned into a vector from which the complete expression cassette is then excised and inserted into an expression vector to allow the expression of the fusion protein in yeast (or any other appropriate expression system). The fusion protein secreted from the yeast can then be collected and purified from the media and tested for its biological activity.

5 For expression in mammalian cell lines, a similar procedure is adopted except that the expression cassette used employs a mammalian promoter, leader sequence and terminator. This expression cassette is then excised and inserted into a plasmid suitable for the transfection of mammalian cell lines.

### 10 *Example 6*

Various interferons can be fused to the N-, C- or N- and C- termini of modified transferrin. These fusions can be constructed using different parts or domains of transferrin such as the N domain or C domain. The proteins can be fused directly or using a linker peptide of various lengths. It is also possible to fuse all or part of the interferon  
15 within the scaffold of transferrin.

A specific example of an interferon that can be fused to Tf is interferon- $\beta$ . The cDNA for the interferon of interest such as IFN  $\beta$  can be isolated by a variety of means such as RT-PCR from mRNA or cDNA, from cDNA libraries, by synthetically constructing the cDNA from overlapping oligonucleotides, by PCR or by other means  
20 known to the art, all using standard methods. The nucleotide sequences for interferons, such as IFN $\alpha$ , IFN $\beta$ , and IFN $\gamma$  are known and available, for instance, in U.S. Patents 5,326,859 and 4,588,585, in EP 32 134, as well as in public databases such as GenBank. The cDNA can be tailored at the 5' and 3' ends to generate restriction sites, such that oligonucleotide linkers can be used to clone the cDNA into a vector containing the cDNA  
25 for modified transferrin. This can be at the N-, C- or N- and C-termini of the transferrin sequence, with or without the use of a spacer sequence. The IFN  $\beta$  (or other interferon) cDNA is cloned into a vector from which the complete expression cassette is then excised and inserted into an expression vector to allow the expression of the fusion protein in yeast. The fusion protein secreted from the yeast can then be collected and purified from  
30 the media and tested for its biological activity.

For expression in mammalian cell lines a similar procedure is adopted except that the expression cassette used employs a mammalian promoter, leader sequence and terminator. This expression cassette is then excised and inserted into a plasmid suitable for the transfection of mammalian cell lines. IFNs fused to transferrin have much longer

half-life, thus, the therapeutic dosages of the fused proteins are much less than the IFNs. Therefore, the fused interferons are more efficacious with much less toxicity.

### ***Example 7***

5 Various single chain antibodies (SCA) were originally invented to simplify antibody selection and production. However, they prove to be of limited or no therapeutic values due to their small size and short *in vivo* half-life. Addition of transferrin to SCA significantly increases the *in vivo* half-life of SCA.

SCA can be fused to the N-, C- or N- and C- termini of modified transferrin.

10 These fusions could also be carried out using different parts or domains of transferrin such as the N domain or C domain. The proteins could be fused directly or using a linker peptide of various length. It is also possible to fuse all or part of the active SCA within the scaffold of transferrin. In such instances the fusion protein is made by inserting the cDNA of the SCA within the cDNA of transferrin for production of the protein in cells. A

15 specific example of a SCA that can be fused to Transferrin is anti-TNF (tumor necrosis factor). Anti-TNF has been used to treat various inflammatory and autoimmune diseases. TNF-SCA could be fused to the N- or C- terminus of modified transferrin in such manner that the coding N-terminus of TNF-SCA is directly attached to the C-terminal amino acid of Transferrin or the C-terminal amino acid of TNF-SCA is directly attached to the N-  
20 terminal amino acid of Transferrin. Alternatively, a peptide linker could be inserted to provide more separation between Transferrin and TNF-SCA and allow more spatial mobility to the two fused proteins. Several examples of TNF-SCA are shown in Figure 4A-4B.

Single chain antibodies are produced by several methods including but not limited  
25 to: selection from phage libraries, cloning of the variable region of a specific antibody by cloning the cDNA of the antibody and using the flanking constant regions as the primer to clone the variable region, or by synthesizing an oligonucleotide corresponding to the variable region of any specific antibody. The cDNA can be tailored at the 5' and 3' ends to generate restriction sites, such that oligonucleotide linkers can be used, for cloning of the  
30 cDNA into a vector containing the cDNA for transferrin. This can be at the N- or C-terminus or N- and C- termini with or without the use of a spacer sequence. The SCA molecule cDNA is cloned into a vector from which the complete expression cassette is then excised and inserted into an expression vector to allow the expression of the fusion protein in yeast. The fusion protein secreted from the yeast can then be collected and

purified from the media and tested for its activity. For expression in mammalian cell lines a similar procedure is adopted except that the expression cassette used employs a mammalian promoter, leader sequence and terminator. This expression cassette is then excised and inserted into a plasmid suitable for the transfection of mammalian cell lines.

- 5 The antibody produced in this manner can be purified from media and tested for its binding to its antigen using standard immunochemical methods.

### ***Example 8***

- CDRs are the variable regions of antibodies that interact with antigens. These  
10 usually consist of relatively short stretches of peptides. Antibodies normally have three CDRs in their heavy chains and three in their light chains. One or more CDRs of an antibody which can interact with the antigen can be fused to modified transferrin to confer antigen binding activity to Transferrin molecule. The CDRs can be fused to the N-, C-, N- and C- termini or engineered into the interior scaffold of transferrin. Examples of the  
15 CDRs sequences from anti-TNF antibodies are shown in the TNF-SCA Figure 4A-4B. cDNAs corresponding to one or more CDRs can be fused with modified transferrin to confer TNF binding activity to transferrin.

### ***Example 9***

- 20 Transferrin fusion technology can also be used to improve the therapeutic properties of peptides that are discovered in various systems such as phage display libraries and peptide libraries. Many of these peptides have biological activities without any homology to natural proteins or peptides. These peptides, due to their short *in vivo* half-lives, are good candidates for fusion to modified transferrin. Because of their small  
25 size they can be fused in variety of regions of transferrin molecule. In addition to the N- and C- termini, they can be inserted in various regions within Transferrin including but not limited to the cystine loops. In this manner the three-dimensional structure of the peptide within transferrin stays relatively rigid. More than one copy of each peptide and more than one peptide can be fused to modified transferrin. Moreover, the peptide sequence  
30 may be used to replace portion of transferrin to confer therapeutic activity to transferrin. Since most of these peptides are short, their cDNA can be synthesized with appropriate restriction sites for insertion into the modified transferrin cDNA. The cDNA could then be inserted in a vector containing the transferrin cDNA in such a manner that the peptide is expressed as part of transferrin or fused to transferrin molecule. Alternatively, PCR

primers could be synthesized that contain the peptide of interest and appropriate section of Transferrin. Using these primers amplification of transferrin cDNA results in the fusion of the peptide to the chosen site on Transferrin. Examples of such peptides are the EPO mimetic peptides: GGTYSCHFGLTWVCKPQGG (SEQ ID NO: 11);

5 DREGCRRGWVGQCKAWFN (SEQ ID NO: 12); and QRVEILEGRTECVLSNLRGRTRY (SEQ ID NO: 30), which have no homology with the natural EPO but have similar biological activities in that they activate the EPO receptor acting as agonists. These peptides also need to have specific conformation for their optimal activity. EPO mimetic peptides can be inserted (or it can replace) in one or more cystine loops of Transferrin. In  
10 this manner Transferrin can acquire EPO activity. Other peptides that can be fused to Transferrin are peptides with binding activity similar to antibodies. These peptides can bind to proteins with relatively high affinity and provide the same biological function as antibodies except their in vivo half-life is very short. Fusion of these peptides to  
15 binding activities. These peptides could be fused to N- or C- terminus or both or within the Transferrin molecule. The peptides can also replace part of transferrin. In addition more than one copy of a peptide or several different peptides could be attached to a single transferrin molecule. An example of such molecule is a peptide that can bind TNF. Attachment of this peptide to Transferrin gives Transferrin the ability to bind TNF and act  
20 similar to anti-TNF antibodies. In this manner antibody like molecules with much easier and economical manufacturing protocol could be made.

### ***Example 10***

Targeted Tf fusion proteins have a combination of two or more proteins or peptides  
25 fused to modified transferrin to serve as a bifunctional molecule. In this case modified transferrin is fused to one protein or peptide to have a new biological activity and to another protein or peptide to targeting. An example of such protein is a transferrin that contains an inhibitory protein such as endostatin and a targeting peptide such as SCA or binding peptide which can recognize tumours. In this manner the inhibitory molecule is  
30 targeted to the tumour where it is needed. The cDNA for the protein of interest can be isolated from cDNA library or can be made synthetically using several overlapping oligonucleotide primers using standard molecular biology methods. The appropriate nucleotides can be engineered in the cDNA to form convenient restriction sites and also allow the attachment of the protein cDNA to transferrin cDNA similar to the method

described for other fusions. Also a targeting protein or peptide cDNA such as single chain antibody or peptides, such as nuclear localization signals, that can direct proteins inside the cells can be fused to the other end or within transferrin. The protein of interest and the targeting peptide is cloned into a vector, which allows the fusion with transferrin cDNA.

5 In this manner both proteins/peptides are fused to modified transferrin. The fused cDNA is then excised and is inserted into an expression vector to allow the expression of the fusion protein in yeast.

All the above procedures can be performed using standard methods in molecular biology. The fusion protein secreted from yeast can be collected and purified from the media and tested for its biological activity and its targeting activity using appropriate biochemical and biological tests. These proteins could also be made in other systems such as mammalian tissue culture using appropriate vector and transfection protocol.

#### *Example 11*

15 The cDNA for the enzyme of interest can be isolated by a variety of means such as RT-PCR from mRNA, from cDNA libraries, by synthetically constructing the cDNA from overlapping oligonucleotides, by PCR or by other means known to the art, all using standard methods. The cDNA can be tailored at the 5' and 3' ends to generate restriction sites, such that oligonucleotide linkers can be used, for cloning of the cDNA into a vector containing the cDNA for modified transferrin. This can be at the N or C-terminus with or without the use of a spacer sequence. The enzyme cDNA is cloned into a vector such from which the complete expression cassette is then excised and inserted an expression vector to allow the expression of the fusion protein in yeast. The fusion protein secreted from the yeast can then be collected and purified from the media and tested for its biological activity. For expression in mammalian cell lines a similar procedure is adopted except that the expression cassette used employs a mammalian promoter, leader sequence and terminator. This expression cassette is then excised and inserted into a plasmid suitable for the transfection of mammalian cell lines.

#### *Example 12*

30 Using phage display, peptides are isolated specific for a specific cell marker on the surface of, for example, a tumor cell. The peptide is then fused to the N-, C- or N- and C-termini of modified transferrin to target the fusion to that specific cell type. The transferrin fusion protein is then loaded with a metal ion which resembles iron in its

transferrin binding properties, but which is cytotoxic, for example gallium or radioactive ions. By this mechanism the gallium or the radioactive ion is targeted to the cell type.

Although the present invention has been described in detail with reference to  
5 examples above, it is understood that various modifications can be made without departing from the spirit of the invention. Accordingly, the invention is limited only by the following claims. All cited patents, patent applications and publications referred to in this application are herein incorporated by reference in their entirety.

**We claim:**

1. A fusion protein comprising a transferrin (Tf) protein exhibiting reduced glycosylation fused to at least one therapeutic protein or peptide.

5

2. A fusion protein of claim 1, wherein the serum half-life of the therapeutic protein or peptide is increased over the serum half-life of the therapeutic protein or peptide in an unfused state.

10

3. A fusion protein of claim 1, wherein the therapeutic protein or peptide is fused to the C-terminal end of Tf.

4. A fusion protein of claim 1, wherein the therapeutic protein or peptide is fused to the N-terminal end of Tf.

15

5. A fusion protein of claim 1, wherein the therapeutic protein or peptide is inserted into at least one loop of the Tf.

6. A fusion protein of claim 1, wherein the Tf protein has reduced affinity for a TfR.

20

7. The fusion protein of claims 1-5, wherein the Tf protein is lacto transferrin (lactoferrin).

8. A fusion protein of claim 6, wherein the TF protein does not bind a TfR.

25

9. A fusion protein of claim 1, wherein the Tf protein has reduced affinity for iron.

10. A fusion protein of claim 9, where the Tf protein does not bind iron.

30

11. A fusion protein of claim 1, wherein said Tf protein comprises at least one mutation that prevents glycosylation.

12. A fusion protein of claim 11, wherein the Tf protein is lacto transferrin (lactoferrin).

13. A fusion protein of claim 1, which is expressed in the presence of  
5 tunicamycin

14. A fusion protein of claim 1, wherein said Tf protein comprises a portion of the N domain of a Tf protein, a bridging peptide and a portion of the C domain of a Tf protein.

15. A fusion protein of claim 14, wherein the bridging peptide links the therapeutic protein or peptide to Tf

16. A fusion protein of claim 14, wherein said therapeutic protein, peptide or polypeptide is inserted between an N and a C domain of Tf protein.

17. A fusion protein of claim 1, wherein the Tf protein have at least one amino acid substitution, deletion or addition in the hinge region.

18. A fusion protein of claim 17, wherein said hinge region is selected from the group consisting of about residue 94 to about residue 96, about residue 245 to about residue 247, about residue 316 to about residue 318, about residue 425 to about residue 427, about residue 581 to about residue 582 and about residue 652 to about residue 658.

19. A fusion protein of claim 1, wherein said Tf protein has at least one amino acid substitution, deletion or addition at a position selected from the group consisting of Asp 63, Gly 65, Tyr 95, Tyr 188, Lys 206, His 207, His 249, Asp 392, Tyr 426, Tyr 514, Tyr 517, His 585, Thr 120, Arg 124, Ala 126, Gly 127, Thr 452, Arg 456, Ala 458 and Gly 459.

20. A fusion protein of claim 5, wherein the therapeutic protein or peptide replaces at least one loop.



21. A fusion protein of claim 11, wherein the glycosylation site is selected from the group consisting of an amino acid residue corresponding to amino acids N413, N611.

22. A fusion protein of claim 6 or 8, wherein the Tf comprises at least one amino acid substitution, deletion or addition at an amino acid residue corresponding to an amino acid selected from the group consisting of Asp 63, Gly 65, Tyr 95, Tyr 188, Lys 206, His 207, His 249, Asp 392, Tyr 426, Tyr 514, Tyr 517, His 585, Thr 120, Arg 124, Ala 126, Gly 127, Thr 452, Arg 456, Ala 458 and Gly 459.

23. A fusion protein comprising a transferrin (Tf) protein exhibiting reduced affinity for a transferrin receptor (TfR) fused to at least one therapeutic protein or peptide.

24. A fusion protein of claim 1, wherein the serum half-life of the therapeutic protein or peptide is increased over the serum half-life of the therapeutic protein or peptide in an unfused state.

25. A fusion protein of claim 1, wherein the therapeutic protein or peptide is fused to the C-terminal end of Tf.

26. A fusion protein of claim 1, wherein the therapeutic protein or peptide is fused to the N-terminal end of Tf.

27. A fusion protein of claim 1, wherein the therapeutic protein or peptide is inserted into at least one loop of the Tf.

28. A fusion protein of claim 23, wherein the TF protein does not bind a TfR.

29. A fusion protein of claim 23, wherein the Tf protein has reduced affinity for iron.

30. A fusion protein of claim 9, wherein the Tf protein does not bind iron.

31. A fusion protein of claim 23, wherein said Tf protein exhibits reduced or no glycosylation.

32. A fusion protein of claim 31, comprising at least one mutation that prevents glycosylation.

5 33. A fusion protein of claim 23, wherein said Tf protein comprises a portion of the N domain of a Tf protein, a bridging peptide and a portion of the C domain of a Tf protein.

10 34. A fusion protein of claim 33, wherein the bridging peptide links the therapeutic protein or peptide to Tf.

35. A fusion protein of claim 33, wherein said therapeutic protein, peptide or polypeptide is inserted between an N and a C domain of Tf protein.

15 36. A fusion protein of claim 23, wherein the Tf protein have at least one amino acid substitution, deletion or addition in the Tf hinge region.

20 37. A fusion protein of claim 36, wherein said hinge region is selected from the group consisting of about residue 94 to about residue 96, about residue 245 to about residue 247, about residue 316 to about residue 318, about residue 425 to about residue 427, about residue 581 to about residue 582 and about residue 652 to about residue 658.

25 38. A fusion protein of claim 23, wherein said Tf protein has at least one amino acid substitution, deletion or addition at a position selected from the group consisting of Asp 63, Gly 65, Tyr 95, Tyr 188, Lys 206, His 207, His 249, Asp 392, Tyr 426, Tyr 514, Tyr 517, His 585, Thr 120, Arg 124, Ala 126, Gly 127, Thr 452, Arg 456, Ala 458 and Gly 459.

30 39. A fusion protein of claim 25, wherein the therapeutic protein or peptide replaces at least one loop.

40. A fusion protein of claim 31, wherein the glycosylation site is selected from the group consisting of an amino acid residue corresponding to amino acids N413, N611.

41. A nucleic acid molecule encoding a fusion protein of either claim 1 or 23.
42. A vector comprising a nucleic acid molecule of claim 41.
- 5 43. A host cell comprising a vector of claim 42.
44. A host cell comprising a nucleic acid molecule of claim 41.
- 10 45. A method of expressing a Tf fusion protein comprising culturing a host cell of claim 43 under conditions which express the encoded fusion protein.
46. A method of expressing a Tf fusion protein comprising culturing a host cell of claim 44 under conditions which express the encoded fusion protein.
- 15 47. A host cell of claim 43, wherein the cell is prokaryotic or eukaryotic.
48. A host cell of claim 44, wherein the cell is prokaryotic or eukaryotic.
49. A host cell of claim 47, wherein the cell is a yeast cell.
- 20 50. A host cell of claim 48, wherein the cell is a yeast cell.
51. A transgenic animal comprising a nucleic acid molecule of 41.
- 25 52. A method of producing a Tf fusion protein comprising isolating a fusion protein from a transgenic animal of claim 51.
53. A method of claim 52, wherein the Tf fusion protein comprises lactoferrin.
- 30 54. A method of claim 53, wherein the fusion protein is isolated from a biological fluid from the transgenic animal.
55. A method of claim 53, wherein the fluid is serum or milk.

56. A method of treating a disease or disease symptom in a patient, comprising the step of administering a fusion protein of claim 1 or claim 23.

**FIGURE 1****Alignment of N and C domains of Transferrin to show Iron Binding residues.**

```

N  --VFD---KTWRNGAVSEHATKQSERDHMKSVTPSDGPSMAQYKKASYLDGTRATAAN
C  PEAPTDECKPKMGALSHHERLKDEWS-----VNSVC-KTECVSAETTEDCTAKMNG

      *                               *

N  EADAVTIDAGLVYDAYLAPNNIKPVVAHFVG----SKEDPQTFYAVAVVVK-DGFGQMN
C  EADAMSNDGCFVYIAGKCG--LVVLAENNNKSDNCEDTLEAGYFAVAVVVKASDLTWD

      † † † †

N  QPRGKKSCHTIGTGRSAGWNLEIGLLYCDIPEPRKPLEKAVANFESGSCAPCADGTDFFQL
C  NIKGKKSCHTAVGRITAGWNLEPMGLLYNKNHCR--FD-----ETISEGCALGSKD--SSL

      *

N  GQLCPGCG---GSTLN--QYECYSCALKCKEKGADYAFVKHSTLFFN-----LANK
C  CKHMGESLNLGEPNNKEGYCYMTCAHGLVE--KEDVAFVKHQLPQNTGGKNPDPWAKN

      *

N  ADRDQVELLGLDNTKQVVEHYKDCHEAQVESHTVARSMSGGKEDLTWELLNOACEHREK-
C  LNEKDVELLGLDGTREKVEHYANGHTARAPNHAVTR--KDEACVHKELRQOHLFGSN

      †

N  --DKSKEFQLESPPHGKDLLHKDSAHGFLKVPPRMDAKMYLGYEYVTAIRNIREGTC---
C  VTCCSGNQCLESERSET-KDLLFRDDTVCLAKLHLDNTYEKYLGEYVYKANGNIRKCSSTSL

N  -----
C  LEACTFRRP

```

Light gray shading: similarity

Dark gray shading: identity

Amino acid residues involved in iron binding (\*).

N domain

Asp 63

Tyr 95

Tyr 188

His 249

C domain

Asp 392

Tyr 426

Tyr 514

His 585

Indirectly involved in iron binding (†)

Lys 296

Arg 632

Binding of carbonate ion (‡)

Thr 120

Arg 124

Ala 126

Gly 127

Thr 452

Arg 456

Ala 458

Gly 459

## FIGURE 2A

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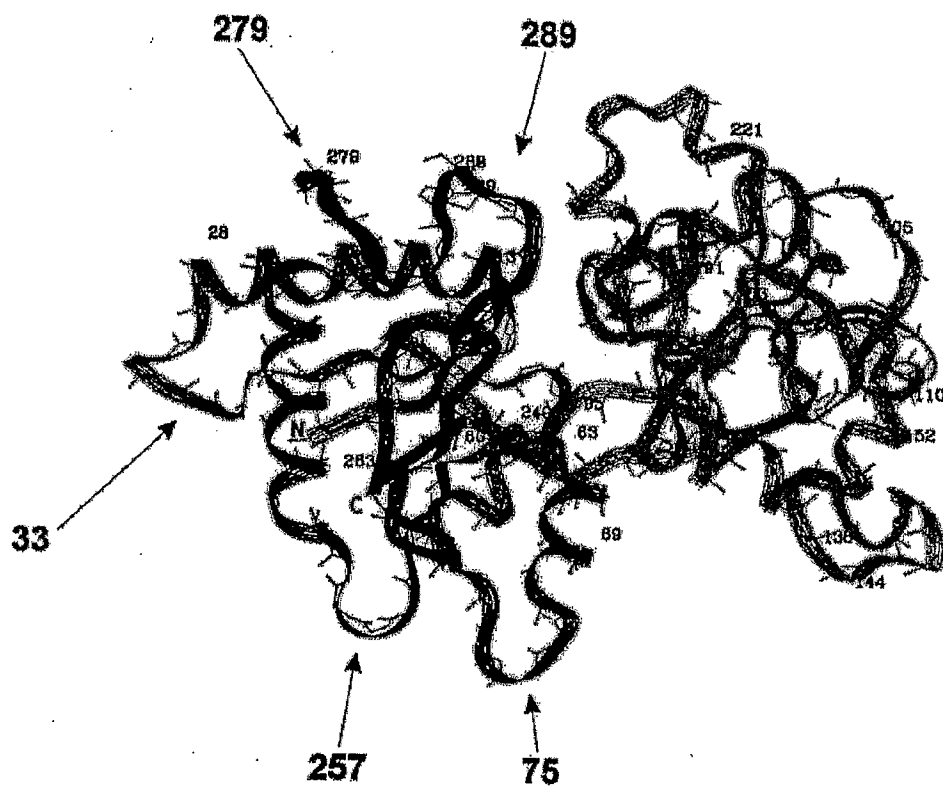
## Alignment of Tf Sequences.

Human	1	-VPDKAVRNCAMSEHEATKQOSTREHNKSVTPSDQESVAGIAGKASMLEGIRAAAHADPA	59
Rabbit	1	-VTEKAVRNCAMVDHEASKCANTRHSKKVTPEDGRITIVKASALLDGCATAAHEAQA	59
Rat	1	-VPDKAVRNCAMSEHENTKQISTREHMTKVPADGRLPQVETSTENQDCAKASGGKADA	59
Mouse	1	-VPDKAVRNCAMSEHENTKQISTREHMTKVPADGRLPQVETSTENQDCAKASGGKADA	59
Horse	1	--AEOLVRNCTVSNHEVSKCAETRESKSTVPA-PPLVACVIRRTSYLEETITADNADPA	57
Bovine	1	-DPERVVRNCTVSTREANCAAFENMLRLES-SEFVSQVKKTSHEMSTHATSNNEADPA	58
Pig	1	-VAQKVRNCTVSNCEANKCSETRNNMSKAVKN-SPLVSCVKKSSVLEETITADNADPA	58
Chicken	1	APPKSVVRNCTVSNFEEKKNNLHILTQQRIS----LITATQKATMLPSTICAAANADPA	56
Human	60	VTHDASLVYDNYLAENNLKRVVADYVSKEDPOTFYAVAVVVRDSCFMMNCTREKSCF	119
Rabbit	60	VTHDASLVHEAGCTENNMLKRVVADYVSKENKRFVAVVAVVVRDSCFMMNCTREKSCF	119
Rat	60	LTHDGSWVYDAGLTENNMLKRVVADYVSKLEHRTFHMLAVAVVVRGTDFTLNQOQKSCF	119
Mouse	60	MTHDGSWVYDAGLTENNMLKRVVADYVSKLEHRTFHMLAVAVVVRGTDFTLNQOQKSCF	119
Horse	58	VTHDASLVHEAGLSYNNMLKRVVADYVSKTEPOTFYAVAVVVRDSCFMMNCTREKSCF	117
Bovine	59	VTHDGSLLVYHAGLKNNMLKRVVADYVSKEDPOTFYAVAVVVRDSCFMMNCTREKSCF	118
Pig	59	VTHDASLVHEAGLSYNNMLKRVVADYVSKEDPOTFYAVAVVVRDSCFMMNCTREKSCF	118
Chicken	57	LSHDGSQAEAGAAFYKNNHAAEVNHTEGSTISYAVAVVVRGTDFTVNDHCHTSCF	116
Human	120	TCGLGRSAGNNIPETLTYCDLHEPRK-----PLEHAYVSTPSGSCVPGADGADTFCOLC	174
Rabbit	120	TCGLGRSAGNNIPETLTYCDLHEPRK-----PLEHAYVSTPSGSCVPGADGADTFCOLC	174
Rat	120	TCGLGRSAGNNIPETLTYCDLHEPRK-----PLEHAYVSTPSGSCVPGADGADTFCOLC	174
Mouse	120	TCGLGRSAGNNIPETLTYCDLHEPRK-----PLEHAYVSTPSGSCVPGADGADTFCOLC	174
Horse	118	TCGLGRSAGNNIPETLTYCDLHEPRK-----PLEHAYVSTPSGSCVPGADGADTFCOLC	172
Bovine	119	TCGLGRSAGNNIPETLTYCDLHEPRK-----PLEHAYVSTPSGSCVPGADGADTFCOLC	173
Pig	119	TCGLGRSAGNNIPETLTYCDLHEPRK-----PLEHAYVSTPSGSCVPGADGADTFCOLC	173
Chicken	117	TCGLGRSAGNNIPETLTYCDLHEPRK-----PLEHAYVSTPSGSCVPGADGADTFCOLC	174
Human	175	PG-----CGSTLNOITGVSGAKKCKDQAGDVATVNHSTTFENHANKADPDONTELLCLD	229
Rabbit	175	PG-----CGSSVOPVGVSGAKKCKDQAGDVATVNHSTTFENHANKADPDONTELLCLD	229
Rat	175	PG-----CGSSPTQPRGVSGAKKCKDQAGDVATVNHSTTFENHANKADPDONTELLCLD	229
Mouse	175	PG-----CGSSSTQPRGVSGAKKCKDQAGDVATVNHSTTFENHANKADPDONTELLCLD	229
Horse	173	VKGTDKCAASNHEPITGVSGAKKCKDQAGDVATVNHSTTFENHANKADPDONTELLCLD	232
Bovine	174	AKGTDKCAASNHEPITGVSGAKKCKDQAGDVATVNHSTTFENHANKADPDONTELLCLD	233
Pig	174	AKGTAEKCAASNHEPITGVSGAKKCKDQAGDVATVNHSTTFENHANKADPDONTELLCLD	233
Chicken	175	KCD--PKTKCARNAFVSGMSGATHELRCKDQAGDVATVNHSTTFENHANKADPDONTELLCLD	230
Human	230	NTRKPVDEKDCYLARVESHAVARSVDGIGEDLLNGLLNQAQOEHEGKDKSKDFOLRSSPH	289
Rabbit	230	NTRKPVDEKDCYLARVESHAVARSVDGIGEDLLNGLLNQAQOEHEGKDKSKDFOLRSSPH	289
Rat	230	NTRKPVDEKDCYLARVESHAVARSVDGIGEDLLNGLLNQAQOEHEGKDKSKDFOLRSSPH	289
Mouse	230	NTRKPVDEKDCYLARVESHAVARSVDGIGEDLLNGLLNQAQOEHEGKDKSKDFOLRSSPH	289
Horse	233	NTRKPVDEKDCYLARVESHAVARSVDGIGEDLLNGLLNQAQOEHEGKDKSKDFOLRSSPH	292
Bovine	234	NTRKPVDDKDCYLARVESHAVARSVDGIGEDLLNGLLNQAQOEHEGKDKSKDFOLRSSPH	293
Pig	234	NTRKPVDDKDCYLARVESHAVARSVDGIGEDLLNGLLNQAQOEHEGKDKSKDFOLRSSPH	293
Chicken	231	GSQGVDDNMTTGNWARVAHAYVARD-DNAYVEDLNSFASKAOSDRGVDTKSEHLEGPRG	289
Human	290	G-----KDLLEKDSAHCEFLKVPVPRMDAKMVEGVNVTALRNLRGTCDEAPTDECKPVK	344
Rabbit	290	G-----KDLLEKDSAHCEFLKVPVPRMDAKMVEGVNVTALRNLRGTCDEAPTDECKPVK	344
Rat	290	G-----KDLLEKDSAHCEFLKVPVPRMDAKMVEGVNVTALRNLRGTCDEAPTDECKPVK	340
Mouse	290	G-----KDLLEKDSAHCEFLKVPVPRMDAKMVEGVNVTALRNLRGTCDEAPTDECKPVK	343
Horse	293	G-----KDLLEKDSAHCEFLKVPVPRMDAKMVEGVNVTALRNLRGTCDEAPTDECKPVK	347
Bovine	294	G-----KDLLEKDSAHCEFLKVPVPRMDAKMVEGVNVTALRNLRGTCDEAPTDECKPVK	347
Pig	294	G-----KDLLEKDSAHCEFLKVPVPRMDAKMVEGVNVTALRNLRGTCDEAPTDECKPVK	348
Chicken	290	KKDPVLKDLLEKDSAHCEFLKVPVPRMDAKMVEGVNVTALRNLRGTCDEAPTDECKPVK	347

## FIGURE 2B

Human	345	CAISLHERRLKGEWSVNSVCKTECVSAETTHEDCTAKIMNGEADAMSLDGGFVYTAGKGGI	404
Rabbit	345	CAISLHERRLKGEWSVTGCLLEECESABTPHDCIAKIMNGEADAMSLDGGYVMTACQAGI	404
Rat	341	CAISHORRAKGEWSVTGNCOTEECESAESTEDCTDKIMNGEADAMSLDGGHAYTACQAGI	400
Mouse	344	CAISLHERRLKGEWSVTIECKLEECESABTHEDCTEKIMNGEADAMSLDGGHAYTACQAGI	403
Horse	348	CAIGAHKVKGEWSVNEGCNLEECESAQSTEDGIAKIMNGEADAMSLDGGFVYTAGKGGI	407
Bovine	348	CAIGHQRRTKCDRNSGFSGGATECEEAENTTECTAKIMNGEADAMSLDGGYVYTAGKGGI	407
Pig	349	CAIGHEETQKCDANSINSGCKLECVSAENTPEDCTAKIMNGEADAMSLDGGYVYTAGKGGI	408
Chicken	348	CAVGKDEKSGDRNSVNSGCDVEGTVDETKOCILIKIMNGEADAMSLDGGYVYTAGKGGI	407
Human	405	VEVLAENYKNS--DNCEDTP-----ACNFAYAVW--KASDLITDNLKCKRSCHTAVGR	456
Rabbit	405	VEVLAENYEST--D-CKKAP-----ECNLSVAVV--KENPDINNNLEKCKRSCHTAVDR	455
Rat	401	VEVMAENYDIS--S-CTNP-QSDVFPKCHYAVAVW--A-SSSTNNNNLEKCKRSCHTAVDR	455
Mouse	404	VEVMAENYESS--N-CAIPSOQGIFFPKCHYAVAVW--A-DSSTNNNNLEKCKRSCHTAVDR	459
Horse	408	VEVLAENYETRSGSAGVDTP-----ECNHAFAVW--KSSSDPDITNNSLEKCKRSCHTAVDR	462
Bovine	408	VEVLAENYKTE-GECKNTPE-----KCNLAFAVW--TSANINNNNLDKCKRSCHTAVDR	460
Pig	409	VEVLAENYKTE-GENGVNTP-----KCNLAFAVW--KSSGPDINNNNLEKCKRSCHTAVDR	462
Chicken	408	VEVMAENYDDE--SQCKTDR---PASFAYAVW--KDSNNNNNNLEKCKRSCHTAVGR	460
Human	457	IACWNIPMGLMNRINHCRTDEEFSEGGAPGSKKESILCKIOMGSGL---NLCEPNNKEG	513
Rabbit	456	IACWNIPMGLMNRINHCRTDEEFROGAPGSKKESILCELTGP-----SVCAPNNREG	510
Rat	456	IACWNIPMGLMNRINHCRTDEEFSSGAPGSKKESILCKIOMGSGL---NLCEPNNKEG	510
Mouse	460	IACWNIPMGLMNRINHCRTDEEFSSGAPGSKKESILCKIOMGSGL---NLCEPNNKEG	514
Horse	463	IACWNIPMGLMNRINHCRTDEEFSSGAPGSKKESILCKIOMGSGL---NLCEPNNKEG	522
Bovine	461	IACWNIPMGLMNRINHCRTDEEFSSGAPGSKKESILCKIOMGSGL---NLCEPNNKEG	520
Pig	463	IACWNIPMGLMNRINHCRTDEEFSSGAPGSKKESILCKIOMGSGL---NLCEPNNKEG	522
Chicken	461	IACWNIPMGLMNRINHCRTDEEFSSGAPGSKKESILCKIOMGSGL---NLCEPNNKEG	520
Human	514	NYGYTGAFRCFLVERGDVAEVKHTVTPONIGCKNPDPWAKNNNEKDYELLGLDGRTRKPVSE	573
Rabbit	511	NYGYTGAFRCFLVERGDVAEVKHTVTPONIGCKNPDPWAKNNNEKDYELLGLDGRTRKPVSE	570
Rat	511	NYGYTGAFRCFLVERGDVAEVKHTVTPONIGCKNPDPWAKNNNEKDYELLGLDGRTRKPVSE	570
Mouse	515	NYGYTGAFRCFLVERGDVAEVKHTVTPONIGCKNPDPWAKNNNEKDYELLGLDGRTRKPVSE	574
Horse	523	NYGYTGAFRCFLVERGDVAEVKHTVTPONIGCKNPDPWAKNNNEKDYELLGLDGRTRKPVSE	582
Bovine	521	NYGYTGAFRCFLVERGDVAEVKHTVTPONIGCKNPDPWAKNNNEKDYELLGLDGRTRKPVSE	580
Pig	523	NYGYTGAFRCFLVERGDVAEVKHTVTPONIGCKNPDPWAKNNNEKDYELLGLDGRTRKPVSE	582
Chicken	521	NYGYTGAFRCFLVERGDVAEVKHTVTPONIGCKNPDPWAKNNNEKDYELLGLDGRTRKPVSE	580
Human	574	YANCHLARAENHNAVSRKDKKACVHKIKROQHLCFQSNVDEGSCNFCLESETKDLLERD	633
Rabbit	571	AHNCILAKAPNHAVSRKDKKACVHKIKROQHLCFQSNVDEGSCNFCLESETKDLLERD	630
Rat	571	FATCILAQAENHNAVSRKDKKACVHKIKROQHLCFQSNVDEGSCNFCLESETKDLLERD	630
Mouse	575	FASCHLARAENHNAVSRKDKKACVHKIKROQHLCFQSNVDEGSCNFCLESETKDLLERD	632
Horse	583	FKSCILARAENHNAVSRKDKKACVHKIKROQHLCFQSNVDEGSCNFCLESETKDLLERD	642
Bovine	581	AENCHLARAENHNAVSRKDKKACVHKIKROQHLCFQSNVDEGSCNFCLESETKDLLERD	640
Pig	583	AENCHLARAENHNAVSRKDKKACVHKIKROQHLCFQSNVDEGSCNFCLESETKDLLERD	642
Chicken	581	YRECNLAEVETHAVVSRPEKANKTRDLLERCKKREGVNGSEKS--KEMMTESQNKDLLERD	639
Human	634	DTKCLVDRIRGKNTYEKYLEGEEVVKAVGNLRKSTSSILLEACTERRP-----	679
Rabbit	631	DTKCLVDRIRGKNTYEKYLEGEEVVKAVGNLRKSTSSILLEACTERRP-----	676
Rat	631	DTKCHTKLEPGTTPPEKYLEGEEVVKAVGNLRKSTSSILLEACTERRP-----	676
Mouse	633	DTKCFVVKLEPGTTPPEKYLEGEEVVKAVGNLRKSTSSILLEACTERRP-----	677
Horse	643	DTKCHLANQPTTTPPEKYLEGEEVVKAVGNLRKSTSSILLEACTERRP-----	688
Bovine	641	DTKCHASTA-KKTYESTLGGDYVRAMINLRKSTSSILLEACTERRP-----	685
Pig	643	DTKCHARVG-KKTYESTLGGDYVRAMINLRKSTSSILLEACTERRP-----	696
Chicken	640	LKRNCFKVRREGTTPPEKYLEGEEVVKAVGNLRKSTSSILLEACTERRP-----	686

**FIGURE 3**





**FIGURE 4A****VH region for anti-TNF $\alpha$  Antibodies.**

			CDR1	CDR2	
VH	1	QVQLVQSGAEVKKPGESLKISCKGHCYSTLSWITGTVROMPKCHHWGLIYP---QDSD			57
P VH	1	EVKLEESCGGLVQPGGEMKLSQVAGCFIENHWMNWFQSPERKCHHWAEIRSKSINSAT			60
33	1	QVQLLESGGGVVQPCRSLRISCAASGFTISSYGMENFCAPEKCHHWAVISYD---SNK			58
35	1	QVQLVQSGAEVKKPGESVKVSCMAAGGTINSEPTNWFCAPEKCHHWGRILPI-ICIAD			59
37	1	QVQLVQSGAEVKKPGESVKVSCMAAGGTISSYATSNWFCAPEKCHHWG-----TSEN			53
39	1	QVQLVQSGGLVQPGGSLRLISCAASGFTISTIVMNTVFCAPCKCHHWVSGHSGG---CGSI			58
			CDR3		
VH	58	TRSPSPFOGQVLSAEKISITAMLOWSSISKASDIAWTCAR-----HWG-----MDV			105
P VH	60	-HVAESVKCRFTLSRDEKSAVLMQMTDIRTEFTGVAQSRN-----YGGST-----YDY			109
33	58	-YVADSVKCRFTLSRDNKNMLLMQMNSTRAEFTFAVTCAKD-----SGDLA-----FEI			107
35	59	--VAQFOGQVMTIADRTSTAMMLRSLISEDFAVTCARPEA--VTVPAP-----LDY			110
37	53	--VAQKFOGQVMTIADRTSTAMMLRSLISEDFAVTCAREVQ--FYHDSSGYLDALDI			109
39	58	-YVADSVKCRFTLSRDNKNMLLMQMNSTRAEFTFAVTCAKDLSNRLSGGGT-----FEI			112
VH	106	WGCHLMVTVS-----			114
P VH	110	WGCHLMVTVS-----			119
33	108	WGCHLMVTVSSGSASAPTLFPLVSCENSPSDTSSVAVGCLAQDFLPDSIIFSWKYKNNSD			167
35	111	WGCHLMVTVSSASTKGPSVFPLAPSSKSTSGG-TAALGCLVKDYFPEPVTVSWN--SGAL			167
37	110	WGCHLMVTVSSASTKGPSVFPLAPSSKSTSGG-TAALGCLVKDYFPEPVTVSWN--SGAL			166
39	113	WGCHLMVTVSSGSASAPTLFPLVSCENSPSDTSSVAVGCLAQDFLPDSITFSWKYKNNSD			172
VH	114	-----			114
P VH	119	-----			119
33	168	ISSTRGFPSVLRGGKYAATSQVLLPSKDVMQGTDEHVCKVQHPNGNKEKNVPLPV-			223
35	168	TSGVHTFPAVLQSSGLYSLSSVVTVPSSSLG--TQTYICNVNHHKPSNTKVDKTVERK			222
37	167	TSGVHTFPAVLQSSGLYSLSSVVTVPSSSLG--TQTYICNVNHHKPSNTKVDKTVERK			221
39	173	ISSTRGFPSVLRGGKYAATSQVLLPSKDVMQGTDEHVCKVQHPNGNKEKNVPLPV-			228

**Key.**

VH VH from synthetic ScFv Accession no: AF288521

P VH VH from US Patent 5,698,195

33 VH from Accession no: AB027433

35 VH from Accession no: AB027435

37 VH from Accession no: AB027437

39 VH from Accession no: AB027439

Dark gray = identity

Light gray = similarity

**FIGURE 4B****VLregion for anti-TNF- Antibodies.**

			CDR1		CDR2	
VL	1	QAVLTG-PSSVSGAPCORVITISCTGSSSNIGAGYDVH		YQQLPETA	KHLYGNSNRPS	59
P VL	1	DILLTQSPAILSVGPCERVVSFCRASOF-VGS--		STHAYOORTNGSPRL	KYASGSM	57
34	1	ELVMTQSPATLSLSPGERATPSCRASQS-VSS--		YLAAYQOKPGQAPRL	YDAGNRAT	57
36	1	DIQMTQSPSTLSAEVQDRVITICRASQS-HSS--		WLAAYQOKPGKAPKHL	YKASGLES	57
38	1	DIELTQSPSTLSAEVQDRVITICRASQS-LNN--		WLAAYQOKPGKAPKHL	YKASLES	57
40	1	DIELTQSPATLSLSPGERATLSGRASQS-VSS--		YLAAYQOKPGQAPRL	INDAGNRAT	57
			CDR3			
VL	60	VEDRFSGSKSCFASLAFTGLQAEDEADYGC	SYDSSLGSGSVTCGGTQLT	VL-----		111
P VL	58	LESRFSGSGSGCDFTLSNTVSEELIADYGC	SHS--WPFTIGSCINLE	YK-----		107
34	58	LEVRFSGSGSGCDFTLTSSLEPEDFAVYGL	LORDN--WPWTEGQGHKVEIKRTVAAPSV			115
36	58	VLSRFSGSGSGCTETLTSSLOPDDFATYGC	QY-N--SYWTEGQGHKVEIKRTVAAPSV			114
38	58	VPSRFSGSASCTETLTSSLOPDDFATYGC	QY-N--SPWTEGQGHKVEIKRTVAAPSV			114
40	58	LEARFSGSGSGCDFTLTSSLEPEDFVVYGL	QORSN--WPLETGQGHKVEIKRTVAAPSV			115
VL	111	-----				111
P VL	107	-----				107
34	116	FIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYS				175
36	115	FIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYS				174
38	115	FIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYS				174
40	116	FIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYS				175
VL	111	-----				111
P VL	107	-----				107
34	176	SSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC				214
36	175	SSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC				213
38	175	SSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC				213
40	176	SSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC				214

**Key.**

VL	VL from synthetic ScFv Accession no: AF288521
P VL	VL from US Patent 5,698,195
34	VL from Accession no: AB027434
36	VL from Accession no: AB027436
38	VL from Accession no: AB027438
40	VL from Accession no: AB027440

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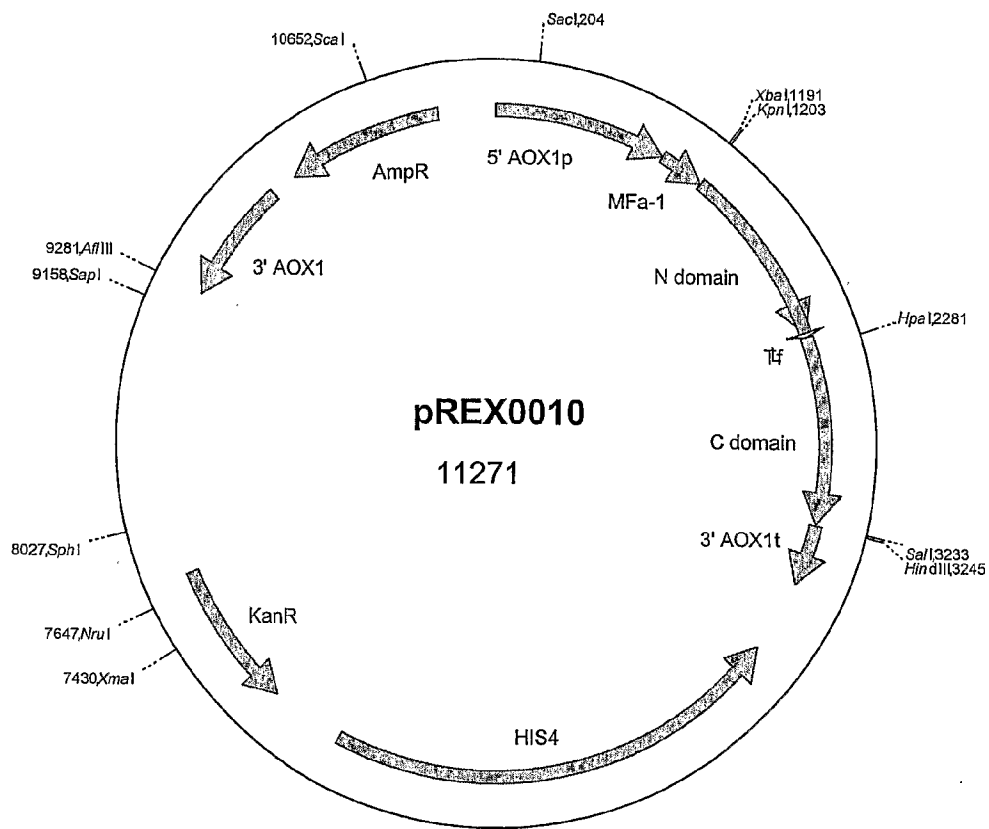


FIGURE 5

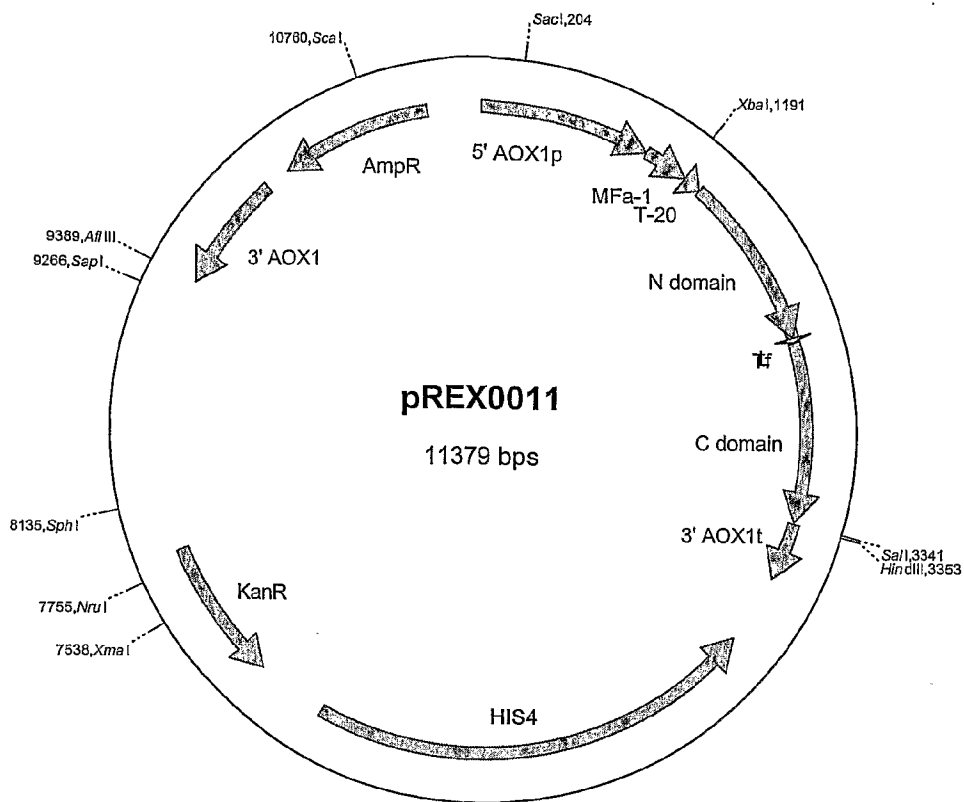


FIGURE 6

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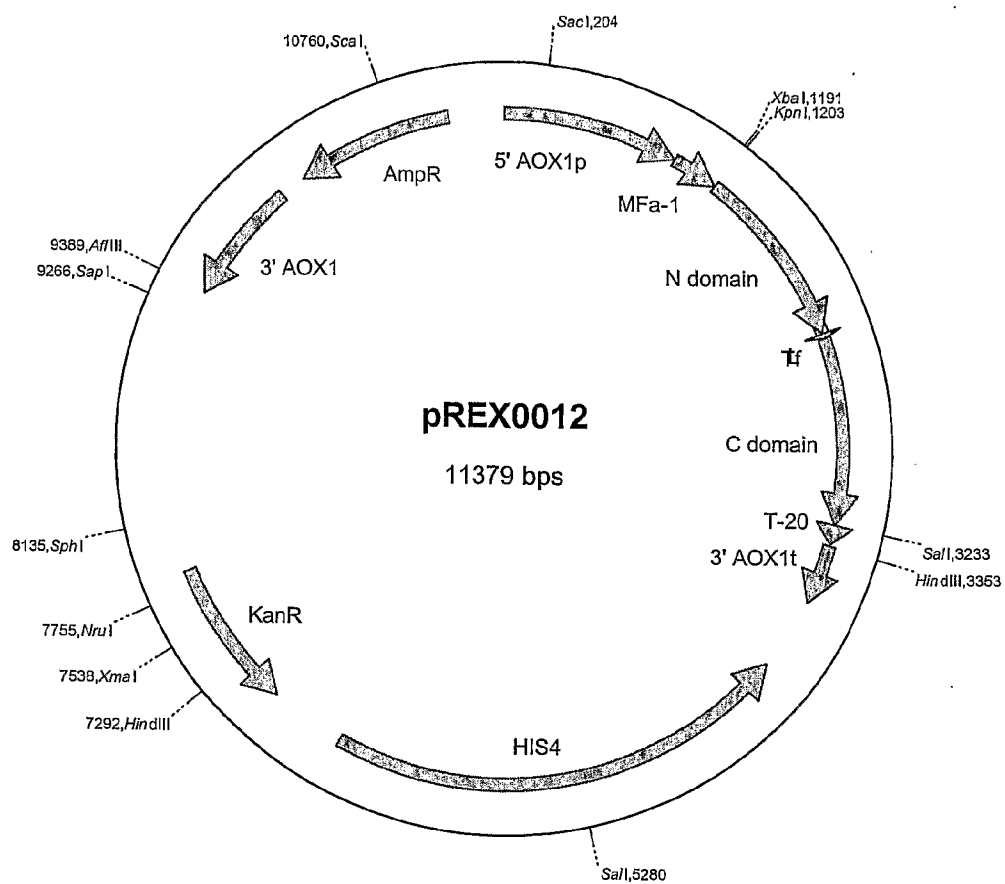


FIGURE 7

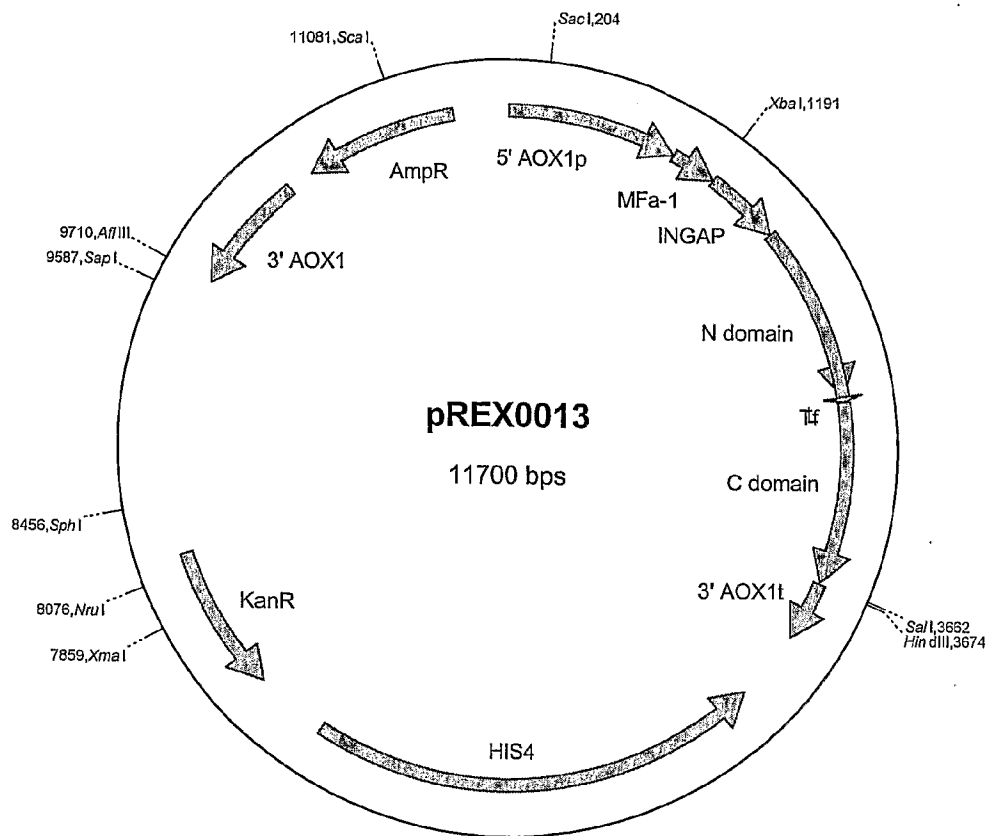


FIGURE 8

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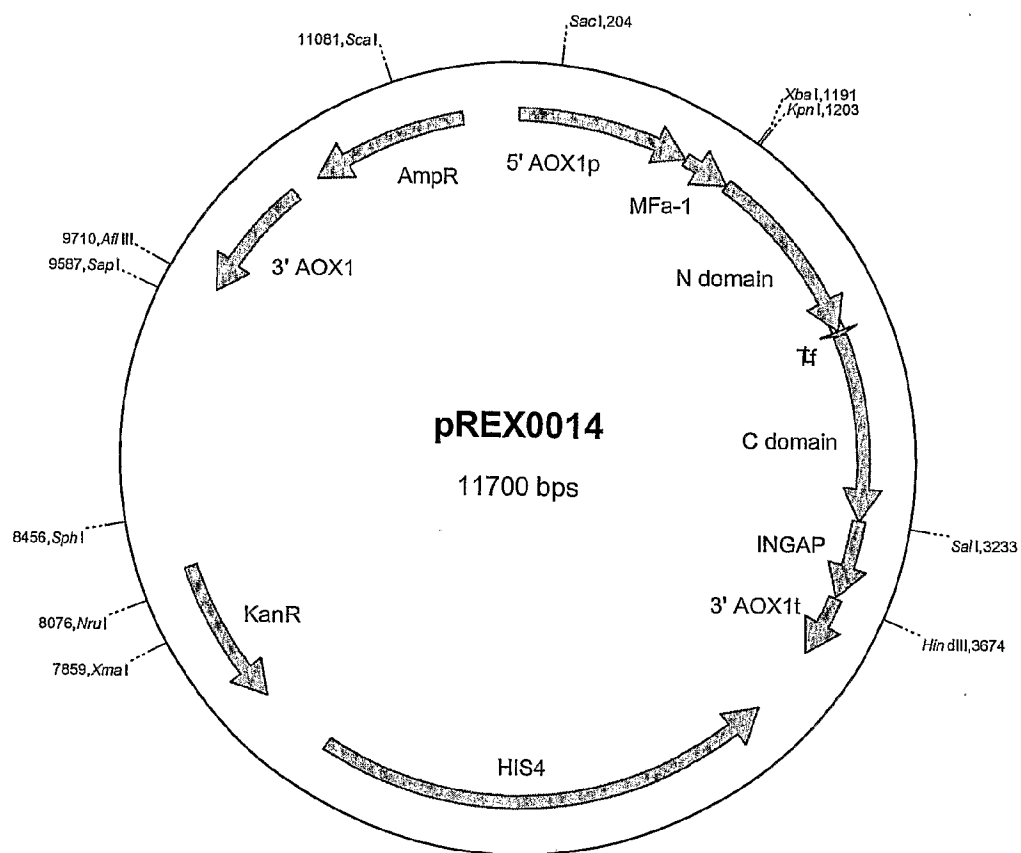


FIGURE 9

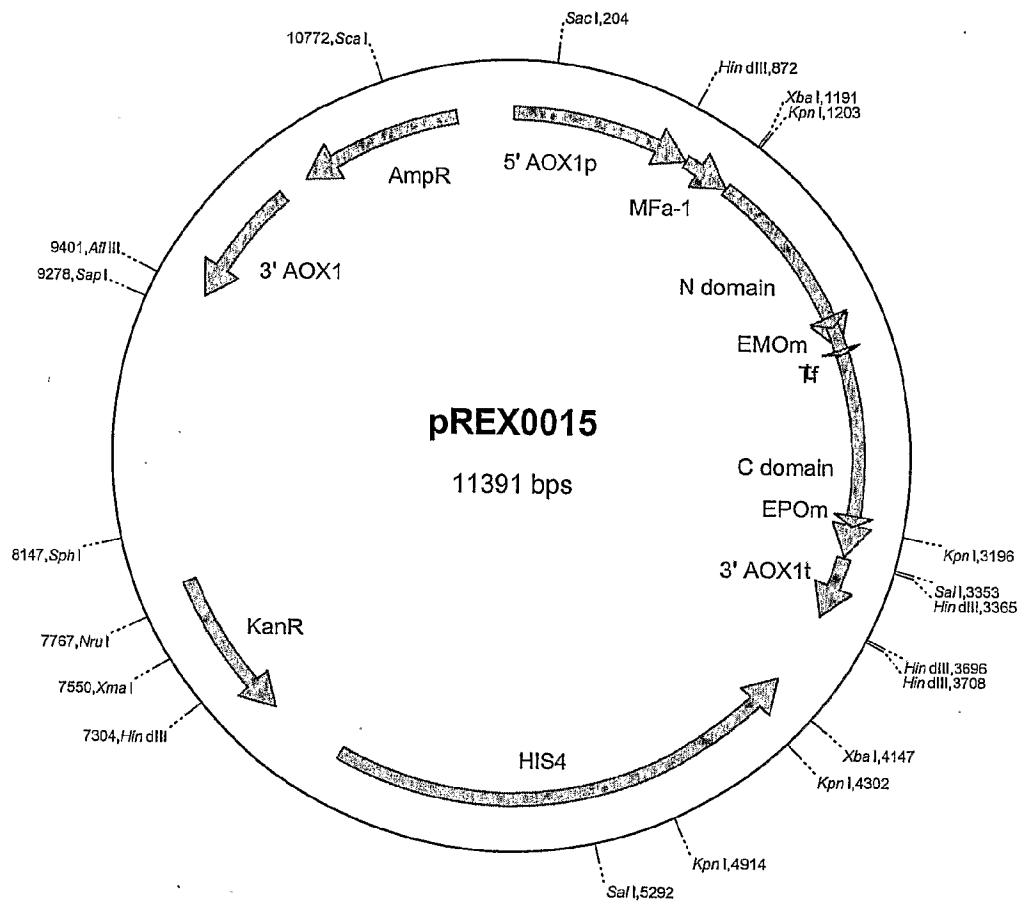


FIGURE 10



## SEQUENCE LISTING

<110> Prior, Christopher P.

<120> Modified Transferrin Fusion Proteins

<130> 54710-5001-WO

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<150> US 60/315,745

<151> 2001-08-30

<150> US 60/334,059

<151> 2001-11-30

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Leu Ala Val Gly Ala Leu Leu Val Cys Ala Val Leu Gly Leu Cys Leu
      5              10              15

gct gtc cct gat aaa act gtg aga tgg tgt gca gtg tcg gag cat gag      152
Ala Val Pro Asp Lys Thr Val Arg Trp Cys Ala Val Ser Glu His Glu
      20              25              30

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      55              60              65

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Cys Ile Arg Ala Ile Ala Ala Asn Glu Ala Asp Ala Val Thr Leu Asp
      70              75              80

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Val Val Ala Glu Phe Tyr Gly Ser Lys Glu Asp Pro Gln Thr Phe Tyr	
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Tyr Ala Val Ala Val Val Lys Lys Asp Ser Gly Phe Gln Met Asn Gln	
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Leu Arg Gly Lys Lys Ser Cys His Thr Gly Leu Gly Arg Ser Ala Gly	
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tgg aac atc ccc ata ggc tta ctt tac tgt gac tta cct gag cca cgt	536
Trp Asn Ile Pro Ile Gly Leu Leu Tyr Cys Asp Leu Pro Glu Pro Arg	
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Met Gly Gly Lys Glu Asp Leu Ile Trp Glu Leu Leu Asn Gln Ala Gln	
275 280 285 290	
gaa cat ttt ggc aaa gac aaa tca aaa gaa ttc caa cta ttc agc tct	968
Glu His Phe Gly Lys Asp Lys Ser Lys Glu Phe Gln Leu Phe Ser Ser	
295 300 305	
cct cat ggg aag gac ctg ctg ttt aag gac tct gcc cac ggg ttt tta	1016
Pro His Gly Lys Asp Leu Leu Phe Lys Asp Ser Ala His Gly Phe Leu	
310 315 320	
aaa gtc ccc ccc agg atg gat gcc aag atg tac ctg ggc tat gag tat	1064

Lys	Val	Pro	Pro	Arg	Met	Asp	Ala	Lys	Met	Tyr	Leu	Gly	Tyr	Glu	Tyr		
		325					330					335					
gtc	act	gcc	atc	cgg	aat	cta	cgg	gaa	ggc	aca	tgc	cca	gaa	gcc	cca	1112	
Val	Thr	Ala	Ile	Arg	Asn	Leu	Arg	Glu	Gly	Thr	Cys	Pro	Glu	Ala	Pro		
	340					345					350						
aca	gat	gaa	tgc	aag	cct	gtg	aag	tgg	tgt	gcg	ctg	agc	cac	cac	gag	1160	
Thr	Asp	Glu	Cys	Lys	Pro	Val	Lys	Trp	Cys	Ala	Leu	Ser	His	His	Glu		
355					360					365					370		
agg	ctc	aag	tgt	gat	gag	tgg	agt	gtt	aac	agt	gta	ggg	aaa	ata	gag	1208	
Arg	Leu	Lys	Cys	Asp	Glu	Trp	Ser	Val	Asn	Ser	Val	Gly	Lys	Ile	Glu		
				375					380					385			
tgt	gta	tca	gca	gag	acc	acc	gaa	gac	tgc	atc	gcc	aag	atc	atg	aat	1256	
Cys	Val	Ser	Ala	Glu	Thr	Thr	Glu	Asp	Cys	Ile	Ala	Lys	Ile	Met	Asn		
			390					395					400				
gga	gaa	gct	gat	gcc	atg	agc	ttg	gat	gga	ggg	ttt	gtc	tac	ata	gcg	1304	
Gly	Glu	Ala	Asp	Ala	Met	Ser	Leu	Asp	Gly	Gly	Phe	Val	Tyr	Ile	Ala		
	405						410					415					
ggc	aag	tgt	ggt	ctg	gtg	cct	gtc	ttg	gca	gaa	aac	tac	aat	aag	agc	1352	
Gly	Lys	Cys	Gly	Leu	Val	Pro	Val	Leu	Ala	Glu	Asn	Tyr	Asn	Lys	Ser		
	420					425					430						
gat	aat	tgt	gag	gat	aca	cca	gag	gca	ggg	tat	ttt	gct	gta	gca	gtg	1400	
Asp	Asn	Cys	Glu	Asp	Thr	Pro	Glu	Ala	Gly	Tyr	Phe	Ala	Val	Ala	Val		
435					440					445					450		
gtg	aag	aaa	tca	gct	tct	gac	ctc	acc	tgg	gac	aat	ctg	aaa	ggc	aag	1448	
Val	Lys	Lys	Ser	Ala	Ser	Asp	Leu	Thr	Trp	Asp	Asn	Leu	Lys	Gly	Lys		
				455					460					465			
aag	tcc	tgc	cat	acg	gca	gtt	ggc	aga	acc	gct	ggc	tgg	aac	atc	ccc	1496	
Lys	Ser	Cys	His	Thr	Ala	Val	Gly	Arg	Thr	Ala	Gly	Trp	Asn	Ile	Pro		
			470					475					480				
atg	ggc	ctg	ctc	tac	aat	aag	atc	aac	cac	tgc	aga	ttt	gat	gaa	ttt	1544	
Met	Gly	Leu	Leu	Tyr	Asn	Lys	Ile	Asn	His	Cys	Arg	Phe	Asp	Glu	Phe		
		485					490					495					
ttc	agt	gaa	ggt	tgt	gcc	cct	ggg	tct	aag	aaa	gac	tcc	agt	ctc	tgt	1592	
Phe	Ser	Glu	Gly	Cys	Ala	Pro	Gly	Ser	Lys	Lys	Asp	Ser	Ser	Leu	Cys		
	500					505					510						
aag	ctg	tgt	atg	ggc	tca	ggc	cta	aac	ctg	tgt	gaa	ccc	aac	aac	aaa	1640	
Lys	Leu	Cys	Met	Gly	Ser	Gly	Leu	Asn	Leu	Cys	Glu	Pro	Asn	Asn	Lys		
515					520					525					530		
gag	gga	tac	tac	ggc	tac	aca	ggc	gct	ttc	agg	tgt	ctg	gtt	gag	aag	1688	
Glu	Gly	Tyr	Tyr	Gly	Tyr	Thr	Gly	Ala	Phe	Arg	Cys	Leu	Val	Glu	Lys		
				535				540						545			
gga	gat	gtg	gcc	ttt	gtg	aaa	cac	cag	act	gtc	cca	cag	aac	act	ggg	1736	
Gly	Asp	Val	Ala	Phe	Val	Lys	His	Gln	Thr	Val	Pro	Gln	Asn	Thr	Gly		
			550					555					560				
gga	aaa	aac	cct	gat	cca	tgg	gct	aag	aat	ctg	aat	gaa	aaa	gac	tat	1784	
Gly	Lys	Asn	Pro	Asp	Pro	Trp	Ala	Lys	Asn	Leu	Asn	Glu	Lys	Asp	Tyr		

565	570	575	
gag ttg ctg tgc ctt gat ggt acc agg aaa cct gtg gag gag tat gcg			1832
Glu Leu Leu Cys Leu Asp Gly Thr Arg Lys Pro Val Glu Glu Tyr Ala			
580	585	590	
aac tgc cac ctg gcc aga gcc ccg aat cac gct gtg gtc aca cgg aaa			1880
Asn Cys His Leu Ala Arg Ala Pro Asn His Ala Val Val Thr Arg Lys			
595	600	605	610
gat aag gaa gct tgc gtc cac aag ata tta cgt caa cag cag cac cta			1928
Asp Lys Glu Ala Cys Val His Lys Ile Leu Arg Gln Gln Gln His Leu			
	615	620	625
ttt gga agc aac gta act gac tgc tcg ggc aac ttt tgt ttg ttc cgg			1976
Phe Gly Ser Asn Val Thr Asp Cys Ser Gly Asn Phe Cys Leu Phe Arg			
	630	635	640
tcg gaa acc aag gac ctt ctg ttc aga gat gac aca gta tgt ttg gcc			2024
Ser Glu Thr Lys Asp Leu Leu Phe Arg Asp Asp Thr Val Cys Leu Ala			
	645	650	655
aaa ctt cat gac aga aac aca tat gaa aaa tac tta gga gaa gaa tat			2072
Lys Leu His Asp Arg Asn Thr Tyr Glu Lys Tyr Leu Gly Glu Glu Tyr			
	660	665	670
gtc aag gct gtt ggt aac ctg aga aaa tgc tcc acc tca tca ctc ctg			2120
Val Lys Ala Val Gly Asn Leu Arg Lys Cys Ser Thr Ser Ser Leu Leu			
	675	680	685
gaa gcc tgc act ttc cgt aga cct taa aatctcagag gtagggctgc			2167
Glu Ala Cys Thr Phe Arg Arg Pro			
	695		
caccaagggtg aagatgggaa cgcagatgat ccatgagttt gccctggttt cactggccca			2227
agtgggtttgt gctaaccacg tctgtcttca cagctctgtg ttgccatgtg tgctgaacaa			2287
aaaataaaaa ttattattga ttttatattt c			2318

<210> 2  
 <211> 698  
 <212> PRT  
 <213> Homo sapiens

<400> 2  
 Met Arg Leu Ala Val Gly Ala Leu Leu Val Cys Ala Val Leu Gly Leu  
 1 5 10 15  
 Cys Leu Ala Val Pro Asp Lys Thr Val Arg Trp Cys Ala Val Ser Glu  
 20 25 30  
 His Glu Ala Thr Lys Cys Gln Ser Phe Arg Asp His Met Lys Ser Val  
 35 40 45  
 Ile Pro Ser Asp Gly Pro Ser Val Ala Cys Val Lys Lys Ala Ser Tyr  
 50 55 60  
 Leu Asp Cys Ile Arg Ala Ile Ala Ala Asn Glu Ala Asp Ala Val Thr  
 65 70 75 80  
 Leu Asp Ala Gly Leu Val Tyr Asp Ala Tyr Leu Ala Pro Asn Asn Leu  
 85 90 95  
 Lys Pro Val Val Ala Glu Phe Tyr Gly Ser Lys Glu Asp Pro Gln Thr  
 100 105 110

Phe Tyr Tyr Ala Val Ala Val Val Lys Lys Asp Ser Gly Phe Gln Met  
 115 120 125  
 Asn Gln Leu Arg Gly Lys Lys Ser Cys His Thr Gly Leu Gly Arg Ser  
 130 135 140  
 Ala Gly Trp Asn Ile Pro Ile Gly Leu Leu Tyr Cys Asp Leu Pro Glu  
 145 150 155 160  
 Pro Arg Lys Pro Leu Glu Lys Ala Val Ala Asn Phe Phe Ser Gly Ser  
 165 170 175  
 Cys Ala Pro Cys Ala Asp Gly Thr Asp Phe Pro Gln Leu Cys Gln Leu  
 180 185 190  
 Cys Pro Gly Cys Gly Cys Ser Thr Leu Asn Gln Tyr Phe Gly Tyr Ser  
 195 200 205  
 Gly Ala Phe Lys Cys Leu Lys Asp Gly Ala Gly Asp Val Ala Phe Val  
 210 215 220  
 Lys His Ser Thr Ile Phe Glu Asn Leu Ala Asn Lys Ala Asp Arg Asp  
 225 230 235 240  
 Gln Tyr Glu Leu Leu Cys Leu Asp Asn Thr Arg Lys Pro Val Asp Glu  
 245 250 255  
 Tyr Lys Asp Cys His Leu Ala Gln Val Pro Ser His Thr Val Val Ala  
 260 265 270  
 Arg Ser Met Gly Gly Lys Glu Asp Leu Ile Trp Glu Leu Leu Asn Gln  
 275 280 285  
 Ala Gln Glu His Phe Gly Lys Asp Lys Ser Lys Glu Phe Gln Leu Phe  
 290 295 300  
 Ser Ser Pro His Gly Lys Asp Leu Leu Phe Lys Asp Ser Ala His Gly  
 305 310 315 320  
 Phe Leu Lys Val Pro Pro Arg Met Asp Ala Lys Met Tyr Leu Gly Tyr  
 325 330 335  
 Glu Tyr Val Thr Ala Ile Arg Asn Leu Arg Glu Gly Thr Cys Pro Glu  
 340 345 350  
 Ala Pro Thr Asp Glu Cys Lys Pro Val Lys Trp Cys Ala Leu Ser His  
 355 360 365  
 His Glu Arg Leu Lys Cys Asp Glu Trp Ser Val Asn Ser Val Gly Lys  
 370 375 380  
 Ile Glu Cys Val Ser Ala Glu Thr Thr Glu Asp Cys Ile Ala Lys Ile  
 385 390 395 400  
 Met Asn Gly Glu Ala Asp Ala Met Ser Leu Asp Gly Gly Phe Val Tyr  
 405 410 415  
 Ile Ala Gly Lys Cys Gly Leu Val Pro Val Leu Ala Glu Asn Tyr Asn  
 420 425 430  
 Lys Ser Asp Asn Cys Glu Asp Thr Pro Glu Ala Gly Tyr Phe Ala Val  
 435 440 445  
 Ala Val Val Lys Lys Ser Ala Ser Asp Leu Thr Trp Asp Asn Leu Lys  
 450 455 460  
 Gly Lys Lys Ser Cys His Thr Ala Val Gly Arg Thr Ala Gly Trp Asn  
 465 470 475 480  
 Ile Pro Met Gly Leu Leu Tyr Asn Lys Ile Asn His Cys Arg Phe Asp  
 485 490 495  
 Glu Phe Phe Ser Glu Gly Cys Ala Pro Gly Ser Lys Lys Asp Ser Ser  
 500 505 510  
 Leu Cys Lys Leu Cys Met Gly Ser Gly Leu Asn Leu Cys Glu Pro Asn  
 515 520 525  
 Asn Lys Glu Gly Tyr Tyr Gly Tyr Thr Gly Ala Phe Arg Cys Leu Val  
 530 535 540  
 Glu Lys Gly Asp Val Ala Phe Val Lys His Gln Thr Val Pro Gln Asn  
 545 550 555 560  
 Thr Gly Gly Lys Asn Pro Asp Pro Trp Ala Lys Asn Leu Asn Glu Lys  
 565 570 575  
 Asp Tyr Glu Leu Leu Cys Leu Asp Gly Thr Arg Lys Pro Val Glu Glu  
 580 585 590  
 Tyr Ala Asn Cys His Leu Ala Arg Ala Pro Asn His Ala Val Val Thr

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      595              600              605
Arg Lys Asp Lys Glu Ala Cys Val His Lys Ile Leu Arg Gln Gln Gln
 610              615              620
His Leu Phe Gly Ser Asn Val Thr Asp Cys Ser Gly Asn Phe Cys Leu
 625              630              635              640
Phe Arg Ser Glu Thr Lys Asp Leu Leu Phe Arg Asp Asp Thr Val Cys
      645              650              655
Leu Ala Lys Leu His Asp Arg Asn Thr Tyr Glu Lys Tyr Leu Gly Glu
      660              665              670
Glu Tyr Val Lys Ala Val Gly Asn Leu Arg Lys Cys Ser Thr Ser Ser
      675              680              685
Leu Leu Glu Ala Cys Thr Phe Arg Arg Pro
 690              695

```

&lt;210&gt; 3

&lt;211&gt; 679

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;223&gt; Mature transferrin protein

&lt;400&gt; 3

```

Val Pro Asp Lys Thr Val Arg Trp Cys Ala Val Ser Glu His Glu Ala
 1              5              10              15
Thr Lys Cys Gln Ser Phe Arg Asp His Met Lys Ser Val Ile Pro Ser
      20              25              30
Asp Gly Pro Ser Val Ala Cys Val Lys Lys Ala Ser Tyr Leu Asp Cys
      35              40              45
Ile Arg Ala Ile Ala Ala Asn Glu Ala Asp Ala Val Thr Leu Asp Ala
 50              55              60
Gly Leu Val Tyr Asp Ala Tyr Leu Ala Pro Asn Asn Leu Lys Pro Val
 65              70              75              80
Val Ala Glu Phe Tyr Gly Ser Lys Glu Asp Pro Gln Thr Phe Tyr Tyr
      85              90              95
Ala Val Ala Val Val Lys Lys Asp Ser Gly Phe Gln Met Asn Gln Leu
      100              105              110
Arg Gly Lys Lys Ser Cys His Thr Gly Leu Gly Arg Ser Ala Gly Trp
      115              120              125
Asn Ile Pro Ile Gly Leu Leu Tyr Cys Asp Leu Pro Glu Pro Arg Lys
      130              135              140
Pro Leu Glu Lys Ala Val Ala Asn Phe Phe Ser Gly Ser Cys Ala Pro
      145              150              155              160
Cys Ala Asp Gly Thr Asp Phe Pro Gln Leu Cys Gln Leu Cys Pro Gly
      165              170              175
Cys Gly Cys Ser Thr Leu Asn Gln Tyr Phe Gly Tyr Ser Gly Ala Phe
      180              185              190

```

Lys Cys Leu Lys Asp Gly Ala Gly Asp Val Ala Phe Val Lys His Ser  
 195 200 205  
 Thr Ile Phe Glu Asn Leu Ala Asn Lys Ala Asp Arg Asp Gln Tyr Glu  
 210 215 220  
 Leu Leu Cys Leu Asp Asn Thr Arg Lys Pro Val Asp Glu Tyr Lys Asp  
 225 230 235 240  
 Cys His Leu Ala Gln Val Pro Ser His Thr Val Val Ala Arg Ser Met  
 245 250 255  
 Gly Gly Lys Glu Asp Leu Ile Trp Glu Leu Leu Asn Gln Ala Gln Glu  
 260 265 270  
 His Phe Gly Lys Asp Lys Ser Lys Glu Phe Gln Leu Phe Ser Ser Pro  
 275 280 285  
 His Gly Lys Asp Leu Leu Phe Lys Asp Ser Ala His Gly Phe Leu Lys  
 290 295 300  
 Val Pro Pro Arg Met Asp Ala Lys Met Tyr Leu Gly Tyr Glu Tyr Val  
 305 310 315 320  
 Thr Ala Ile Arg Asn Leu Arg Glu Gly Thr Cys Pro Glu Ala Pro Thr  
 325 330 335  
 Asp Glu Cys Lys Pro Val Lys Trp Cys Ala Leu Ser His His Glu Arg  
 340 345 350  
 Leu Lys Cys Asp Glu Trp Ser Val Asn Ser Val Gly Lys Ile Glu Cys  
 355 360 365  
 Val Ser Ala Glu Thr Thr Glu Asp Cys Ile Ala Lys Ile Met Asn Gly  
 370 375 380  
 Glu Ala Asp Ala Met Ser Leu Asp Gly Gly Phe Val Tyr Ile Ala Gly  
 385 390 395 400  
 Lys Cys Gly Leu Val Pro Val Leu Ala Glu Asn Tyr Asn Lys Ser Asp  
 405 410 415  
 Asn Cys Glu Asp Thr Pro Glu Ala Gly Tyr Phe Ala Val Ala Val Val  
 420 425 430  
 Lys Lys Ser Ala Ser Asp Leu Thr Trp Asp Asn Leu Lys Gly Lys Lys  
 435 440 445  
 Ser Cys His Thr Ala Val Gly Arg Thr Ala Gly Trp Asn Ile Pro Met  
 450 455 460  
 Gly Leu Leu Tyr Asn Lys Ile Asn His Cys Arg Phe Asp Glu Phe Phe  
 465 470 475 480  
 Ser Glu Gly Cys Ala Pro Gly Ser Lys Lys Asp Ser Ser Leu Cys Lys  
 485 490 495  
 Leu Cys Met Gly Ser Gly Leu Asn Leu Cys Glu Pro Asn Asn Lys Glu  
 500 505 510  
 Gly Tyr Tyr Gly Tyr Thr Gly Ala Phe Arg Cys Leu Val Glu Lys Gly

515	520	525
Asp Val Ala Phe Val Lys His Gln Thr Val Pro Gln Asn Thr Gly Gly		
530	535	540
Lys Asn Pro Asp Pro Trp Ala Lys Asn Leu Asn Glu Lys Asp Tyr Glu		
545	550	555
560		
Leu Leu Cys Leu Asp Gly Thr Arg Lys Pro Val Glu Glu Tyr Ala Asn		
565	570	575
Cys His Leu Ala Arg Ala Pro Asn His Ala Val Val Thr Arg Lys Asp		
580	585	590
Lys Glu Ala Cys Val His Lys Ile Leu Arg Gln Gln Gln His Leu Phe		
595	600	605
Gly Ser Asn Val Thr Asp Cys Ser Gly Asn Phe Cys Leu Phe Arg Ser		
610	615	620
Glu Thr Lys Asp Leu Leu Phe Arg Asp Asp Thr Val Cys Leu Ala Lys		
625	630	635
640		
Leu His Asp Arg Asn Thr Tyr Glu Lys Tyr Leu Gly Glu Glu Tyr Val		
645	650	655
Lys Ala Val Gly Asn Leu Arg Lys Cys Ser Thr Ser Ser Leu Leu Glu		
660	665	670
Ala Cys Thr Phe Arg Arg Pro		
675		

<210> 4  
 <211> 36  
 <212> PRT  
 <213> Human immunodeficiency virus

<220>  
 <223> Antifusogenic peptide

<400> 4
Phe Trp Asn Trp Leu Ser Ala Trp Lys Asp Leu Glu Leu Leu Glu Gln
1 5 10 15
Glu Asn Lys Glu Gln Gln Asn Gln Ser Glu Glu Ile Leu Ser His Ile
20 25 30
Leu Ser Thr Tyr
35

<210> 5  
 <211> 35  
 <212> PRT  
 <213> Human respiratory syncytial virus

<220>  
 <223> Antifusogenic peptide

<400> 5



Val Tyr Pro Ser Asp Glu Tyr Asp Ala Ser Ile Ser Gln Val Asn Glu  
 1 5 10 15  
 Glu Ile Asn Gln Ala Leu Ala Tyr Ile Arg Lys Ala Asp Glu Leu Leu  
 20 25 30  
 Glu Asn Val  
 35

<210> 6  
 <211> 51  
 <212> PRT  
 <213> Human respiratory syncytial virus

<220>  
 <223> Antifusogenic peptide

<400> 6  
 Ala Val Ser Lys Val Leu His Leu Glu Gly Glu Val Asn Lys Ile Lys  
 1 5 10 15  
 Ser Ala Leu Leu Ser Thr Asn Lys Ala Val Val Ser Leu Ser Asn Gly  
 20 25 30  
 Val Ser Val Leu Thr Ser Lys Val Leu Asp Leu Lys Asn Tyr Ile Asp  
 35 40 45  
 Lys Gln Leu  
 50

<210> 7  
 <211> 35  
 <212> PRT  
 <213> Human respiratory syncytial virus

<220>  
 <223> Antifusogenic peptide

<400> 7  
 Val Phe Pro Ser Asp Glu Phe Asp Ala Ser Ile Ser Gln Val Asn Glu  
 1 5 10 15  
 Lys Ile Asn Gln Ser Leu Ala Phe Ile Arg Glu Ser Asp Glu Leu Leu  
 20 25 30  
 His Asn Val  
 35

<210> 8  
 <211> 12  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <223> Lactoferrin splice variant sequence

<400> 8  
 Glu Asp Cys Ile Ala Leu Lys Gly Glu Ala Asp Ala

1 5 10

<210> 9  
 <211> 27  
 <212> DNA  
 <213> Artificial Sequence

<220>  
 <223> Description of Artificial Sequence:  
 Oligonucleotide for mutagenesis

<400> 9  
 gcagaaaact acgataagag cgataat 27

<210> 10  
 <211> 27  
 <212> DNA  
 <213> Artificial Sequence

<220>  
 <223> Description of Artificial Sequence:  
 Oligonucleotide for mutagenesis

<400> 10  
 ctatttgga ggcacgtaac tgactgc 27

<210> 11  
 <211> 20  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Description of Artificial Sequence: EPO mimetic  
 peptide

<400> 11  
 Gly Gly Thr Tyr Ser Cys His Phe Gly Pro Leu Thr Trp Val Cys Lys  
 1 5 10 15

Pro Gln Gly Gly  
 20

<210> 12  
 <211> 18  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Description of Artificial Sequence: EPO mimetic  
 peptide

<400> 12  
 Asp Arg Glu Gly Cys Arg Arg Gly Trp Val Gly Gln Cys Lys Ala Trp  
 1 5 10 15

Phe Asn

<210> 13  
 <211> 108  
 <212> DNA  
 <213> Artificial Sequence

<220>  
 <223> Description of Artificial Sequence: HIV  
 antifusogenic sequences

<220>  
 <221> CDS  
 <222> (1)..(108)

<400> 13  
 tac aca agc tta ata cac tcc tta att gaa gaa tcg caa aac cag caa 48  
 Tyr Thr Ser Leu Ile His Ser Leu Ile Glu Glu Ser Gln Asn Gln Gln  
     1                    5                    10                    15  
  
 gaa aag aat gaa caa gaa tta ttg gaa tta gat aaa tgg gca agt ttg 96  
 Glu Lys Asn Glu Gln Glu Leu Leu Glu Leu Asp Lys Trp Ala Ser Leu  
                     20                    25                    30  
  
 tgg aat tgg ttt 108  
 Trp Asn Trp Phe  
             35

<210> 14  
 <211> 36  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Description of Artificial Sequence: HIV  
 antifusogenic sequences

<400> 14  
 Tyr Thr Ser Leu Ile His Ser Leu Ile Glu Glu Ser Gln Asn Gln Gln  
     1                    5                    10                    15  
  
 Glu Lys Asn Glu Gln Glu Leu Leu Glu Leu Asp Lys Trp Ala Ser Leu  
                     20                    25                    30  
  
 Trp Asn Trp Phe  
             35

<210> 15  
 <211> 124  
 <212> DNA  
 <213> Artificial Sequence

<220>  
 <223> Description of Artificial Sequence: HIV  
 antifusogenic sequences for fusion proteins

<220>  
 <221> CDS

&lt;222&gt; (1)..(123)

&lt;400&gt; 15

```

cta gag aaa agg tac act agc tta ata cac tcc tta att gaa gaa tcg   48
Leu Glu Lys Arg Tyr Thr Ser Leu Ile His Ser Leu Ile Glu Glu Ser
  1             5             10             15

caa aac cag caa gaa aag aat gaa caa gaa tta ttg gaa tta gat aaa   96
Gln Asn Gln Gln Glu Lys Asn Glu Gln Glu Leu Leu Glu Leu Asp Lys
          20             25             30

tgg gca agt ttg tgg aat tgg ttt gta c                               124
Trp Ala Ser Leu Trp Asn Trp Phe Val
      35             40

```

&lt;210&gt; 16

&lt;211&gt; 41

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

<223> Description of Artificial Sequence: HIV  
antifusogenic sequences for fusion proteins

&lt;400&gt; 16

```

Leu Glu Lys Arg Tyr Thr Ser Leu Ile His Ser Leu Ile Glu Glu Ser
  1             5             10             15

Gln Asn Gln Gln Glu Lys Asn Glu Gln Glu Leu Leu Glu Leu Asp Lys
          20             25             30

Trp Ala Ser Leu Trp Asn Trp Phe Val
      35             40

```

&lt;210&gt; 17

&lt;211&gt; 174

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;223&gt; INGAP protein

&lt;400&gt; 17

```

Met Met Leu Pro Met Thr Leu Cys Arg Met Ser Trp Met Leu Leu Ser
  1             5             10             15

Cys Leu Met Phe Leu Ser Trp Val Glu Gly Glu Glu Ser Gln Lys Lys
          20             25             30

Leu Pro Ser Ser Arg Ile Thr Cys Pro Gln Gly Ser Val Ala Tyr Gly
      35             40             45

Ser Tyr Cys Tyr Ser Leu Ile Leu Ile Pro Gln Thr Trp Ser Asn Ala
      50             55             60

Glu Leu Ser Cys Gln Met His Phe Ser Gly His Leu Ala Phe Leu Leu
      65             70             75             80

```

Ser Thr Gly Glu Ile Thr Phe Val Ser Ser Leu Val Lys Asn Ser Leu  
85 90 95

Thr Ala Tyr Gln Tyr Ile Trp Ile Gly Leu His Asp Pro Ser His Gly  
100 105 110

Thr Leu Pro Asn Gly Gly Trp Lys Trp Ser Ser Ser Asn Val Leu Thr  
115 120 125

Phe Tyr Asn Trp Glu Arg Asn Pro Ser Ile Ala Ala Asp Arg Gly Tyr  
130 135 140

Cys Ala Val Leu Ser Gln Lys Ser Gly Phe Gln Lys Trp Arg Asp Phe  
145 150 155 160

Asn Cys Glu Asn Glu Leu Pro Tyr Ile Cys Lys Phe Lys Val  
165 170

&lt;210&gt; 18

&lt;211&gt; 525

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

<223> Description of Artificial Sequence: INGAP  
sequences

&lt;220&gt;

&lt;221&gt; CDS

&lt;222&gt; (1)..(525)

&lt;400&gt; 18

atg atg ttg cca atg act ttg tgt aga atg tct tgg atg ttg ttg tct 48  
Met Met Leu Pro Met Thr Leu Cys Arg Met Ser Trp Met Leu Leu Ser  
1 5 10 15

tgt ttg atg ttt ttg tct tgg gtt gaa ggt gaa gaa tct caa aaa aaa 96  
Cys Leu Met Phe Leu Ser Trp Val Glu Gly Glu Glu Ser Gln Lys Lys  
20 25 30

ttg cca tct tct aga att act tgt cca caa ggt tct gtt gct tat ggt 144  
Leu Pro Ser Ser Arg Ile Thr Cys Pro Gln Gly Ser Val Ala Tyr Gly  
35 40 45

tct tat tgt tat tct ttg att ttg att cca caa act tgg tct aat gct 192  
Ser Tyr Cys Tyr Ser Leu Ile Leu Ile Pro Gln Thr Trp Ser Asn Ala  
50 55 60

gaa ttg tct tgt caa atg cat ttt tct ggt cat ttg gct ttt ttg ttg 240  
Glu Leu Ser Cys Gln Met His Phe Ser Gly His Leu Ala Phe Leu Leu  
65 70 75 80

tct act ggt gaa att act ttt gtt tct tct ttg gtt aaa aat tct ttg 288  
Ser Thr Gly Glu Ile Thr Phe Val Ser Ser Leu Val Lys Asn Ser Leu  
85 90 95

act gct tat caa tat att tgg att ggt ttg cat gat cca tct cat ggt 336  
Thr Ala Tyr Gln Tyr Ile Trp Ile Gly Leu His Asp Pro Ser His Gly  
100 105 110

act ttg cca aat ggt tct ggt tgg aaa tgg tct tct tct aat gtt ttg 384  
 Thr Leu Pro Asn Gly Ser Gly Trp Lys Trp Ser Ser Ser Asn Val Leu  
           115                                  120                                  125

act ttt tat aat tgg gaa aga aat cca tct att gct gct gat aga ggt 432  
 Thr Phe Tyr Asn Trp Glu Arg Asn Pro Ser Ile Ala Ala Asp Arg Gly  
           130                                  135                                  140

tat tgt gct gtt ttg tct caa aaa tct ggt ttt caa aaa tgg aga gat 480  
 Tyr Cys Ala Val Leu Ser Gln Lys Ser Gly Phe Gln Lys Trp Arg Asp  
           145                                  150                                  155                                  160

ttt aat tgt gaa aat gaa ttg cca tat att tgt aaa ttt aaa gtt 525  
 Phe Asn Cys Glu Asn Glu Leu Pro Tyr Ile Cys Lys Phe Lys Val  
                                   165                                  170                                  175

<210> 19

<211> 175

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: INGAP  
 sequences

<400> 19

Met Met Leu Pro Met Thr Leu Cys Arg Met Ser Trp Met Leu Leu Ser  
           1                                  5                                  10                                  15

Cys Leu Met Phe Leu Ser Trp Val Glu Gly Glu Glu Ser Gln Lys Lys  
                                   20                                  25                                  30

Leu Pro Ser Ser Arg Ile Thr Cys Pro Gln Gly Ser Val Ala Tyr Gly  
                                   35                                  40                                  45

Ser Tyr Cys Tyr Ser Leu Ile Leu Ile Pro Gln Thr Trp Ser Asn Ala  
           50                                  55                                  60

Glu Leu Ser Cys Gln Met His Phe Ser Gly His Leu Ala Phe Leu Leu  
           65                                  70                                  75                                  80

Ser Thr Gly Glu Ile Thr Phe Val Ser Ser Leu Val Lys Asn Ser Leu  
                                   85                                  90                                  95

Thr Ala Tyr Gln Tyr Ile Trp Ile Gly Leu His Asp Pro Ser His Gly  
                                   100                                  105                                  110

Thr Leu Pro Asn Gly Ser Gly Trp Lys Trp Ser Ser Ser Asn Val Leu  
           115                                  120                                  125

Thr Phe Tyr Asn Trp Glu Arg Asn Pro Ser Ile Ala Ala Asp Arg Gly  
           130                                  135                                  140

Tyr Cys Ala Val Leu Ser Gln Lys Ser Gly Phe Gln Lys Trp Arg Asp  
           145                                  150                                  155                                  160

Phe Asn Cys Glu Asn Glu Leu Pro Tyr Ile Cys Lys Phe Lys Val  
                                   165                                  170                                  175

<210> 20  
 <211> 445  
 <212> DNA  
 <213> Artificial Sequence

<220>  
 <223> Description of Artificial Sequence: INGAP  
 sequences for fusion proteins

<220>  
 <221> CDS  
 <222> (1)..(444)

<400> 20  
 cta gag aaa agg ttg cca tct tcc aga att act tgt cca caa ggt tct 48  
 Leu Glu Lys Arg Leu Pro Ser Ser Arg Ile Thr Cys Pro Gln Gly Ser  
 1 5 10 15  
 gtt gct tat ggt tct tat tgt tat tct ttg att ttg att cca caa act 96  
 Val Ala Tyr Gly Ser Tyr Cys Tyr Ser Leu Ile Leu Ile Pro Gln Thr  
 20 25 30  
 tgg tct aat gct gaa ttg tct tgt caa atg cat ttt tct ggt cat ttg 144  
 Trp Ser Asn Ala Glu Leu Ser Cys Gln Met His Phe Ser Gly His Leu  
 35 40 45  
 gct ttt ttg ttg tct act ggt gaa att act ttt gtt tct tct ttg gtt 192  
 Ala Phe Leu Leu Ser Thr Gly Glu Ile Thr Phe Val Ser Ser Leu Val  
 50 55 60  
 aaa aat tct ttg act gct tat caa tat att tgg att ggt ttg cat gat 240  
 Lys Asn Ser Leu Thr Ala Tyr Gln Tyr Ile Trp Ile Gly Leu His Asp  
 65 70 75 80  
 cca tct cat ggt act ttg cca aat ggt tct ggt tgg aaa tgg tct tct 288  
 Pro Ser His Gly Thr Leu Pro Asn Gly Ser Gly Trp Lys Trp Ser Ser  
 85 90 95  
 tct aat gtt ttg act ttt tac aat tgg gaa aga aat cca tct att gct 336  
 Ser Asn Val Leu Thr Phe Tyr Asn Trp Glu Arg Asn Pro Ser Ile Ala  
 100 105 110  
 gct gat aga ggt tat tgt gct gtt ttg tct caa aaa tct ggt ttt caa 384  
 Ala Asp Arg Gly Tyr Cys Ala Val Leu Ser Gln Lys Ser Gly Phe Gln  
 115 120 125  
 aaa tgg aga gat ttt aat tgt gaa aat gaa ttg cca tat att tgt aaa 432  
 Lys Trp Arg Asp Phe Asn Cys Glu Asn Glu Leu Pro Tyr Ile Cys Lys  
 130 135 140  
 ttt aaa gtt gta c 445  
 Phe Lys Val Val  
 145

<210> 21  
 <211> 148  
 <212> PRT  
 <213> Artificial Sequence

&lt;220&gt;

<223> Description of Artificial Sequence: INGAP  
sequences for fusion proteins

&lt;400&gt; 21

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Leu Glu Lys Arg Leu Pro Ser Ser Arg Ile Thr Cys Pro Gln Gly Ser
 1           5           10           15
Val Ala Tyr Gly Ser Tyr Cys Tyr Ser Leu Ile Leu Ile Pro Gln Thr
          20           25           30
Trp Ser Asn Ala Glu Leu Ser Cys Gln Met His Phe Ser Gly His Leu
          35           40           45
Ala Phe Leu Leu Ser Thr Gly Glu Ile Thr Phe Val Ser Ser Leu Val
          50           55           60
Lys Asn Ser Leu Thr Ala Tyr Gln Tyr Ile Trp Ile Gly Leu His Asp
          65           70           75           80
Pro Ser His Gly Thr Leu Pro Asn Gly Ser Gly Trp Lys Trp Ser Ser
          85           90           95
Ser Asn Val Leu Thr Phe Tyr Asn Trp Glu Arg Asn Pro Ser Ile Ala
          100          105          110
Ala Asp Arg Gly Tyr Cys Ala Val Leu Ser Gln Lys Ser Gly Phe Gln
          115          120          125
Lys Trp Arg Asp Phe Asn Cys Glu Asn Glu Leu Pro Tyr Ile Cys Lys
          130          135          140
Phe Lys Val Val
145

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&lt;210&gt; 22

&lt;211&gt; 441

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

<223> Description of Artificial Sequence: INGAP  
sequences for fusion proteins

&lt;220&gt;

&lt;221&gt; CDS

&lt;222&gt; (2)..(436)

&lt;400&gt; 22

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t cga cct ttg cca tct tcc aga att act tgt cca caa ggt tct gtt gct 49
  Arg Pro Leu Pro Ser Ser Arg Ile Thr Cys Pro Gln Gly Ser Val Ala
    1           5           10           15
tat ggt tct tat tgt tat tct ttg att ttg att cca caa act tgg tct 97
Tyr Gly Ser Tyr Cys Tyr Ser Leu Ile Leu Ile Pro Gln Thr Trp Ser
          20           25           30
aat gct gaa ttg tct tgt caa atg cat ttt tct ggt cat ttg gct ttt 145
Asn Ala Glu Leu Ser Cys Gln Met His Phe Ser Gly His Leu Ala Phe

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35	40	45	
ttg ttg tct act ggt gaa att act ttt gtt tct tct ttg gtt aaa aat			193
Leu Leu Ser Thr Gly Glu Ile Thr Phe Val Ser Ser Leu Val Lys Asn			
50	55	60	
tct ttg act gct tat caa tat att tgg att ggt ttg cat gat cca tct			241
Ser Leu Thr Ala Tyr Gln Tyr Ile Trp Ile Gly Leu His Asp Pro Ser			
65	70	75	80
cat ggt act ttg cca aat ggt tct ggt tgg aaa tgg tct tct tct aat			289
His Gly Thr Leu Pro Asn Gly Ser Gly Trp Lys Trp Ser Ser Ser Asn			
85	90	95	
gtt ttg act ttt tac aat tgg gaa aga aat cca tct att gct gct gat			337
Val Leu Thr Phe Tyr Asn Trp Glu Arg Asn Pro Ser Ile Ala Ala Asp			
100	105	110	
aga ggt tat tgt gct gtt ttg tct caa aaa tct ggt ttt caa aaa tgg			385
Arg Gly Tyr Cys Ala Val Leu Ser Gln Lys Ser Gly Phe Gln Lys Trp			
115	120	125	
aga gat ttt aat tgt gaa aat gaa ttg cca tat att tgt aaa ttt aaa			433
Arg Asp Phe Asn Cys Glu Asn Glu Leu Pro Tyr Ile Cys Lys Phe Lys			
130	135	140	
gtt taata			441
Val			
145			

&lt;210&gt; 23

&lt;211&gt; 145

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

<223> Description of Artificial Sequence: INGAP  
sequences for fusion proteins

&lt;400&gt; 23

Arg Pro Leu Pro Ser Ser Arg Ile Thr Cys Pro Gln Gly Ser Val Ala		
1	5	10
15		
Tyr Gly Ser Tyr Cys Tyr Ser Leu Ile Leu Ile Pro Gln Thr Trp Ser		
20	25	30
35	40	45
Asn Ala Glu Leu Ser Cys Gln Met His Phe Ser Gly His Leu Ala Phe		
50	55	60
Ser Leu Thr Ala Tyr Gln Tyr Ile Trp Ile Gly Leu His Asp Pro Ser		
65	70	75
80		
His Gly Thr Leu Pro Asn Gly Ser Gly Trp Lys Trp Ser Ser Ser Asn		
85	90	95
Val Leu Thr Phe Tyr Asn Trp Glu Arg Asn Pro Ser Ile Ala Ala Asp		
100	105	110

Arg Gly Tyr Cys Ala Val Leu Ser Gln Lys Ser Gly Phe Gln Lys Trp  
 115 120 125

Arg Asp Phe Asn Cys Glu Asn Glu Leu Pro Tyr Ile Cys Lys Phe Lys  
 130 135 140

Val  
 145

<210> 24  
 <211> 60  
 <212> DNA  
 <213> Artificial Sequence

<220>  
 <223> Description of Artificial Sequence: EPO mimetic  
 sequences

<220>  
 <221> CDS  
 <222> (1)..(60)

<400> 24  
 ggt ggt act tac tct tgt cat ttt ggt cca ttg act tgg gtt tgt aag 48  
 Gly Gly Thr Tyr Ser Cys His Phe Gly Pro Leu Thr Trp Val Cys Lys  
 1 5 10 15

cca caa ggt ggt 60  
 Pro Gln Gly Gly  
 20

<210> 25  
 <211> 20  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Description of Artificial Sequence: EPO mimetic  
 sequences

<400> 25  
 Gly Gly Thr Tyr Ser Cys His Phe Gly Pro Leu Thr Trp Val Cys Lys  
 1 5 10 15

Pro Gln Gly Gly  
 20

<210> 26  
 <211> 47  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Description of Artificial Sequence: Transferrin  
 peptide insertion region

&lt;400&gt; 26

Asp Lys Ser Lys Glu Phe Gln Leu Phe Ser Ser Pro His Gly Lys Asp  
 1 5 10 15

Leu Leu Phe Lys Asp Ser Ala His Gly Phe Leu Lys Val Pro Pro Arg  
 20 25 30

Met Asp Ala Lys Met Tyr Leu Gly Tyr Glu Tyr Val Thr Ala Ile  
 35 40 45

&lt;210&gt; 27

&lt;211&gt; 49

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

<223> Description of Artificial Sequence: Transferrin  
 peptide insertion region

&lt;400&gt; 27

Asn Val Thr Asp Cys Ser Gly Asn Phe Cys Leu Phe Arg Ser Glu Thr  
 1 5 10 15

Lys Asp Leu Leu Phe Arg Asp Asp Thr Val Cys Leu Ala Lys Leu His  
 20 25 30

Asp Arg Asn Thr Tyr Glu Lys Tyr Leu Gly Glu Glu Tyr Val Lys Ala  
 35 40 45

Val

&lt;210&gt; 28

&lt;211&gt; 140

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

<223> Description of Artificial Sequence: Transferrin  
 DNA sequence for peptide insertion region

&lt;400&gt; 28

agacaaatca aaagaatttc aactattcag ctctcctcat ggtggtactt actcttgta 60  
 ttttggtcca ttgacttggg tttgtaagcc acaaggtggt gggaaggacc tgctgtttaa 120  
 ggactctgcc cacgggtttt 140

&lt;210&gt; 29

&lt;211&gt; 210

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

<223> Description of Artificial Sequence: Transferrin  
 DNA sequence for peptide insertion region

&lt;400&gt; 29

cctatttga agcaacgtaa ctgactgctc gggcaacttt tgtttgttcc ggtcggaagg 60

tggtacttac ttttgtcatt ttggtccatt gacttgggtt tgtaagccac aaggtggtac 120  
caaggacctt ctgttcagag atgacacagt atgtttggcc aaacttcatg acagaaacac 180  
atatgaaaaa tacttaggag aagaatatgt 210

<210> 30

<211> 23

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: EPO mimetic  
peptide

<400> 30

Gln Arg Val Glu Ile Leu Glu Gly Arg Thr Glu Cys Val Leu Ser Asn  
1 5 10 15

Leu Arg Gly Arg Thr Arg Tyr  
20

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/27637

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(7) : C07K 1/00, 14/00, 17/00; C07H 21/04; C12N 15/00, 15/09, 15/63, 15/70, 15/74, 5/00, 5/02; C12P 21/00, 21/04; A01K 67/00, 67/033; A61K 39/00, 39/38

US CL : 530/350; 536/23.4; 435/320.1, 325, 70.1; 800/13, 4, 5, 7; 424/184.1

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 530/350; 536/23.4; 435/320.1, 325, 70.1; 800/13, 4, 5, 7; 424/184.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
WEST, MEDLINE, BIOSIS, EMBASE, SCISEARCH, CAPLUS**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	NEWTON, D.L. et al. Antitransferrin receptor antibody-RNase fusion protein expressed in the mammary gland of transgenic mice. J. Immunol. Meth. 1999, Vol. 231, pages 159-167, see entire document.	1-6, 8-56
Y	PARK, E. et al. Production and characterization of fusion proteins containing transferrin and nerve growth factor. J. Drug Tar. 1998, Vol. 6, No. 1, pages 53-64, see entire document.	1-6, 8-56
Y	PRINCE, L.S. et al. Efficient endocytosis of the cystic fibrosis transmembrane conductance regulator requires a tyrosine-based signal. J. Biol. Chem. 05 February 1999, Vol. 274, No. 6, pages 3602-3609, see entire document.	1-6, 8-56
Y	SHIN, S.U. et al. Transferrin-antibody fusion proteins are effective in brain targeting. PNAS, 1995, Vol. 92, pages 2820-2824, see entire document.	1-6, 8-56

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:	
"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E" earlier application or patent published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

07 December 2002 (07.12.2002)

Date of mailing of the international search report

04 FEB 2003

Name and mailing address of the ISA/US

Commissioner of Patents and Trademarks  
Box PCT  
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

Peter Paras, Jr.

Telephone No. (703) 308-1235

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/27637

## Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claim Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claim Nos.: 7  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.